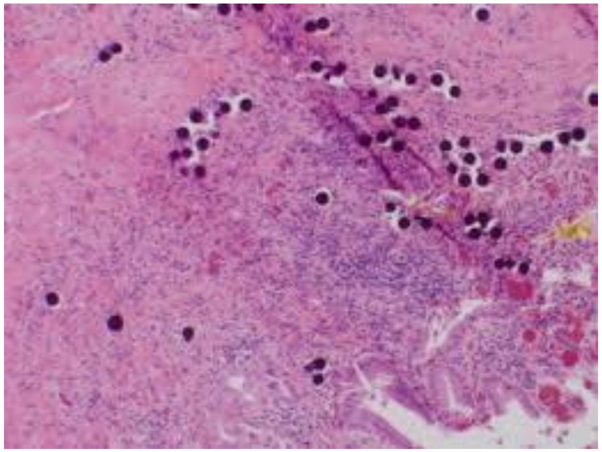
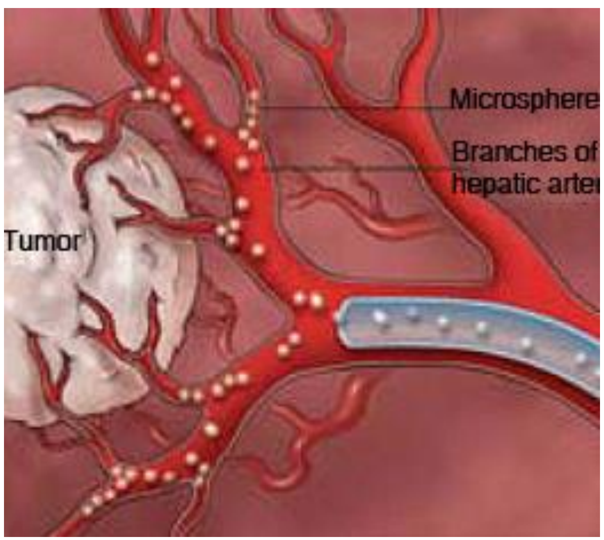




SIRT: Overview of Potential Side-effects and Use of Y90 PET

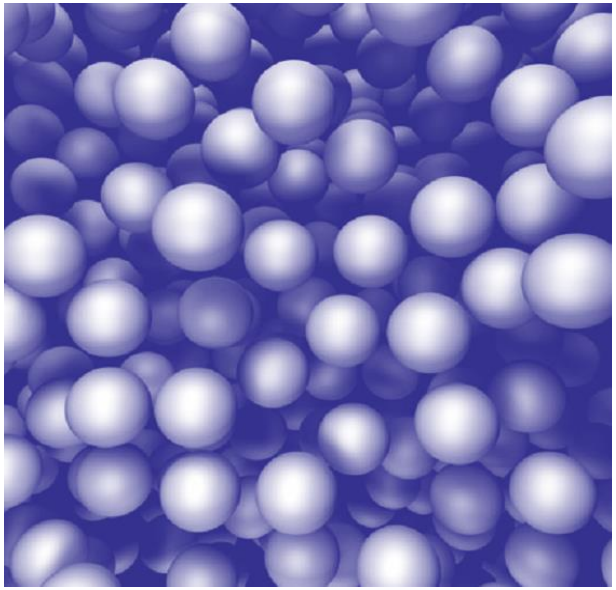
David Chee-Eng Ng
Head and Senior Consultant
Department of Nuclear Medicine and Molecular Imaging
Singapore General Hospital

Scope of talk

- Potential side-effects of Y90 microspheres
- Imaging Y90 microspheres
- Clinical Uses of Y90 PETCT
- Qualitative and Quantitative aspects
- Y90 PET Dosimetry
- Some recommendations on Y90 PET imaging

Disclosures: grants from Merck, Sirtex, Bayer, Genzyme

Y-90 microspheres



TheraSphere® Glass microspheres

2,500 Bq/sphere
1-2 million spheres per treatment

SIR-Spheres® Resin microspheres

50 Bq/sphere
30–60 million spheres per treatment

20 – 60 µm diameter (average diameter 30-40 µm) trapped by small capillary vessels.

Biocompatible but not biodegradable

Y90 Half-life 64.1 hrs (2.67 days)

Y90 Mean beta energy	0.9367 MeV
average penetration	2.5 mm (in tissues)
maximum range	11.0 mm (in tissues)

Targetted delivery of radiation
Delivers >90% of its energy in 11 days.

Classification of Potential Side-effects

Pulmonary
- *Radiation pneumonitis*
- *Atelectasis*
- *Pleural effusion*

Gastrointestinal
- *Ulceration*
- *Pancreatitis*

Hepatobiliary
- *Radiation induced liver disease-REILD*
- *Radiation cholecystitis*
- *Fibrosis*
- *Portal hypertension*

Dermatological
- *Radiation dermatitis*

Hematological
- *Thrombocytopenia*
- *Lymphopenia*

Miscellaneous
- *Splenic radiation*
- *Diaphragmatic perforation*

Vascular
- *Prior TACE & vessel dissection*
- *Antineoangiogenic Rx and stasis*

Pulmonary

Case: *Presented with progressive shortness of breath 6 weeks after whole liver Y90 Rx for bilobar infiltrative HCC. No previous underlying pulmonary disease. Dx of radiation pneumonitis was made after excluding other causes. No pathology.*

A. Technetium 99m-MAA planar Scintigraphy shows avid tumor uptake in the liver, L>R. Lung uptake was relatively low
B. Bremsstrahlung fused SPECT/CT shows satisfactory tumor localization within both lobes
C. CXR 6 weeks post Y90 treatment shows bilateral ground-glass changes + interstitial changes in a relatively symmetric distribution
D. CT chest axial lung windows shows widespread ground glass changes + interlobular septal thickening + intralobular reticular thickening
E. CT coronal reformat shows the distribution of the interstitial pneumonitis with relative sparing of the lower lobes

Tc99m-MAA SPECT scan: Calculated Lung-shunt fraction = *12.5%*
Artery-specific SPECT-CT MIRD dosimetry was performed for dose calculation
Total of *2.80 GBq* of Y90 resin microspheres were divided into 3 portions & injected via right, left & middle hepatic artery
Predicted mean radiation dose to lungs from RHA + MHA + LHA Y90 microspheres injections = *21.2Gy*

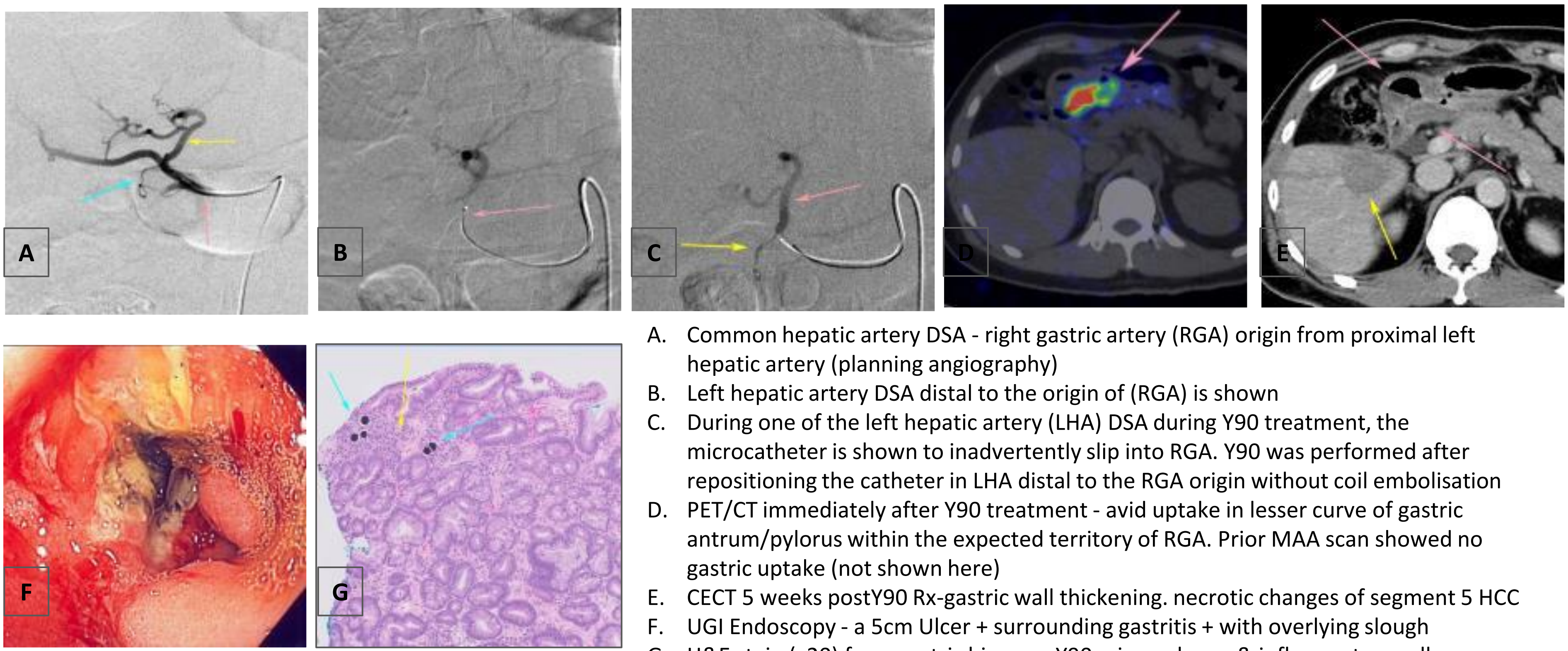
Gastrointestinal

- Incidence 2.9 to 4.8%
- Ulcer starts on serosal site
- Resistant to proton pump inhibitors & >50% require surgical interventions
- IACT review is highly valuable @ identifying unexpected anatomical variants
- SPECT/CT MAA is more sensitive than planar imaging @ detecting gastric uptake
- Occasionally, SPECT/CT may show unexpected gastric uptake not seen on the planning angiography or IACT; these cases may warrant re-angiography or Rx cancellation
- Diagnostic pitfalls:
    - *Free pertechnetate on SPECT/CT*
    - *Misregistration on SPECT/CT*

Murthy R. RG 2005;25:S41-S55

Gastrointestinal

Case: *Presented with worsening epigastric pain 5 weeks after Y90 Rx with resin based Y90 microspheres for bilobar HCCs.*



A. Common hepatic artery DSA - right gastric artery (RGA) origin from proximal left hepatic artery (planning angiography)
B. Left hepatic artery DSA distal to the origin of (RGA) is shown
C. During one of the left hepatic artery (LHA) DSA during Y90 treatment, the microcatheter is shown to inadvertently slip into RGA. Y90 was performed after repositioning the catheter in LHA distal to the RGA origin without coil embolisation
D. PET/CT immediately after Y90 treatment - avid uptake in lesser curve of gastric antrum/pylorus within the expected territory of RGA. Prior MAA scan showed no gastric uptake (not shown here)
E. CECT 5 weeks postY90 Rx-gastric wall thickening. necrotic changes of segment 5 HCC
F. UGI Endoscopy - a 5cm Ulcer + surrounding gastritis + with overlying slough
G. H&E stain (x20) from gastric biopsy – Y90 microspheres & inflammatory cells

Lessons: *Y90 microsphere reflux + unstable catheter position + close proximity of RGA to injection site! Rule of thumb- if the intended site of Y90 Rx is less than 1cm from a gastric branch, it may warrant embolization prior to Y90 microspheres injection*

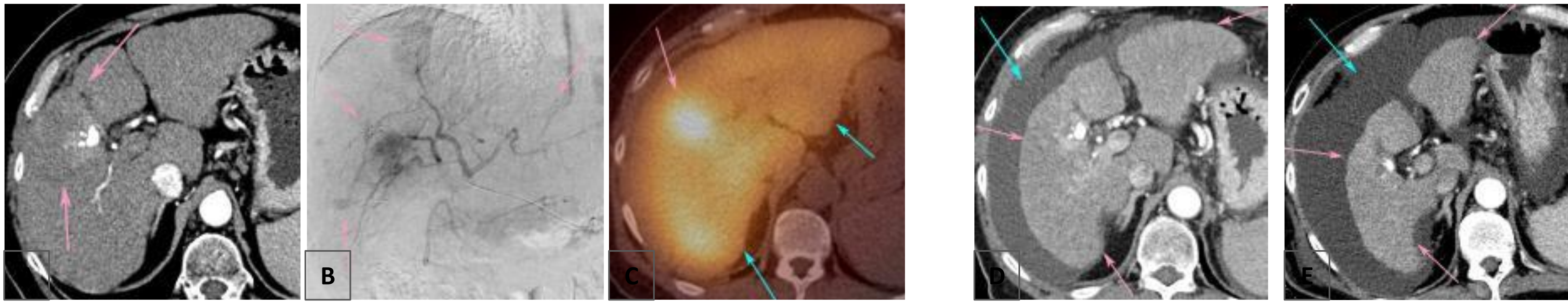
Hepatobiliary

- Incidence of Radioembolization induced liver disease (REILD) is 0-5% in large studies
- Usually 4-8 weeks after radioembolization
- Jaundice, mild ascites, elevated bilirubin & alkaline phosphatase
- Pathologically, sinusoidal obstruction or hepatic veno-occlusive (VOD) disease
- Risk factors:
  - ✓ *Pre-existing liver dysfunction/cirrhosis*
  - ✓ *Previous radioembolization or external radiotherapy*
  - ✓ *Single session whole lobe treatment > than sequential lobar Rx @ 6 weeks interval*
- Other hepatobiliary complications like clinically significant hepatic fibrosis, portal hypertension, hepatic abscess, cholecystitis & biliary stricture are very rare

Lm MG et al. CVIR 2013;36:1536-47

Hepatobiliary

REILD: *Presented with liver decompensation after whole liver Y90 microspheres Rx for bilobar HCC; Child Pugh score B 7 @ the time of consideration for Y90 Rx. Previous TACE x 2 & Deranged LFTs after TACEs had stabilized prior to radioembolization*



January 2016 | February 2016 | February 2016 | April 2016 | June 2016

A. CECT arterial phase shows enhancing HCC in segment 5 with lipoidol from previous TACE. HCCs were seen in left lobe as well. No ascites
B. Planning angiography @ the time of MAA injection shows multifocal hypervascular HCCs
C. Fused SPECT/CT Bremsstrahlung shows whole liver uptake with satisfactory localization of Y90 microspheres in tumors
D. CECT arterial phase @ 6 weeks after Y90 shows new ascites & global volume reduction of the cirrhotic liver
E. CECT arterial phase @ 12 weeks post-Y90 shows further decompensation with marked increase in ascites & further loss of liver volume. Patient failed to respond to medical management and died subsequently from liver failure

Artery-specific SPECT-CT MIRD dosimetry was performed for dose calculation

Right hepatic artery 1.3 GBq & Left hepatic artery 0.55 GBq

Predicted mean radiation dose right TNR= 91:70 Gy & on left TNR=65:64 Gy

Sangro B. Cancer 2008;112:1538-1546

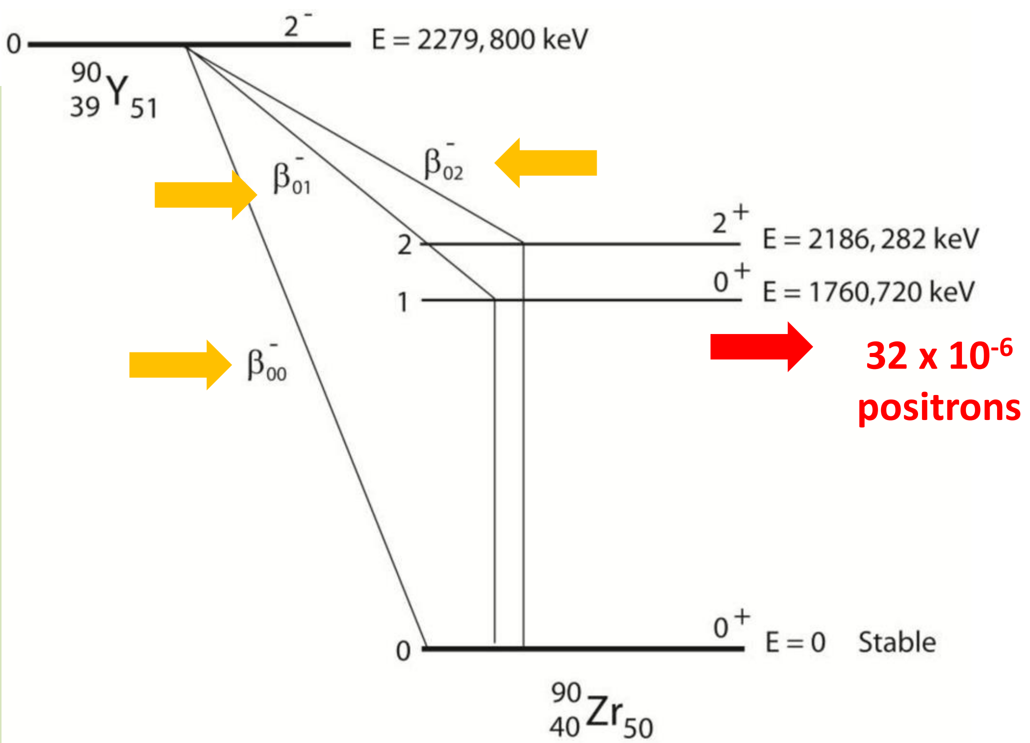
Y-90 microspheres imaging

Production:
Y89 (n,γ) Y90

Decay:
Y90 → Zr90

Beta-emitter (99.98%)

Minimal internal pair-production (32 ppm)
→ positrons (PET)



Conventional imaging from Y90

Imaging Y90 in gamma scanner

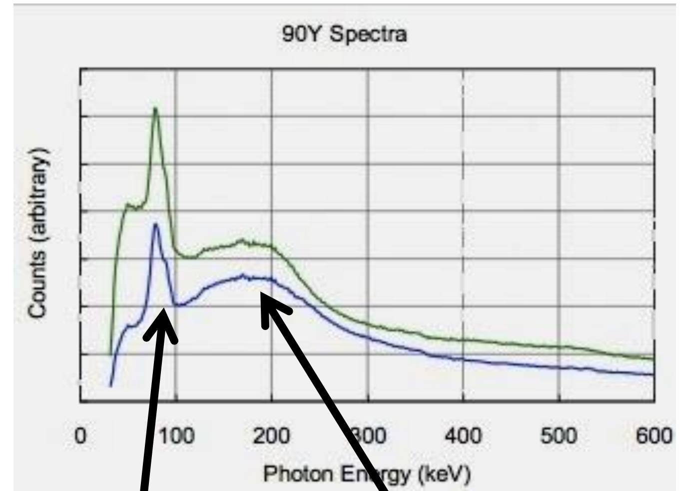
Beta radiation from Y90 scatter in tissue → Bremsstrahlung radiation.

Bremsstrahlung X-rays scatter off the lead collimator →
Pb K-characteristic X-rays at about 80 keV

Gamma scanner energy window is centred at the Pb K-characteristic peak for imaging. This peak is broad and with low counts.

Hence, resolution and lesion detectability poor as image is made from:

1. Bremsstrahlung radiation - is poor in energy resolution
2. Secondary scattered radiation from the Pb collimator – poor spatial resolution



Continuous Bremsstrahlung from tissue and Compton scatter spectrum

Pb K-characteristic X-rays

1955
physics

Ford KW. Phys Rev 98:1516–1517 (1955)

Predicted 0+ Level in $_{40}Zr^{90*\dagger}$

KENNETH W. FORD
Indiana University, Bloomington, Indiana
(Received March 21, 1955)

VERY many nuclear properties exhibit regularities which show clearly the effects of closing of major shells (4, 8, 20, 28, 50, 82, 126)—most notable of these

2005
phantom

Assaying and PET Imaging of Ytrrium-90: 1>>34ppm>0

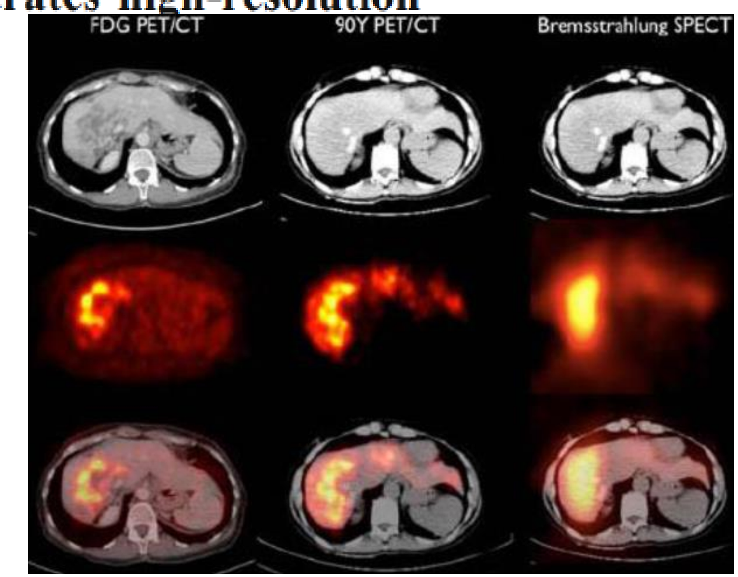
R.J. Nickles, A.D. Roberts, J.A. Nye, A.K. Converse, T.E. Barnhart, M.A. Avila-Rodriguez, R. Sundaresan, D.W. Dick, R.J. Hammas, and B.R. Thomadsen
University of Wisconsin
Madison, WI USA

2009
patient

Yttrium-90 TOF PET scan demonstrates high-resolution biodistribution after liver SIRT

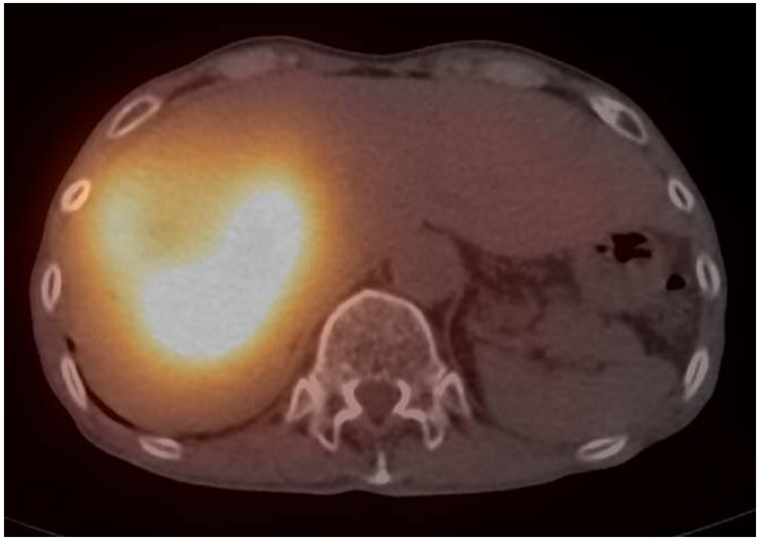
Eur J Nucl Med Mol Imaging (2009) 36:1696

Renaud Lhommel · Pierre Goffette · Marc Van den Eynde · François Jamar · Stanislas Pauwels · Jose I. Bilbao · Stephan Walrand

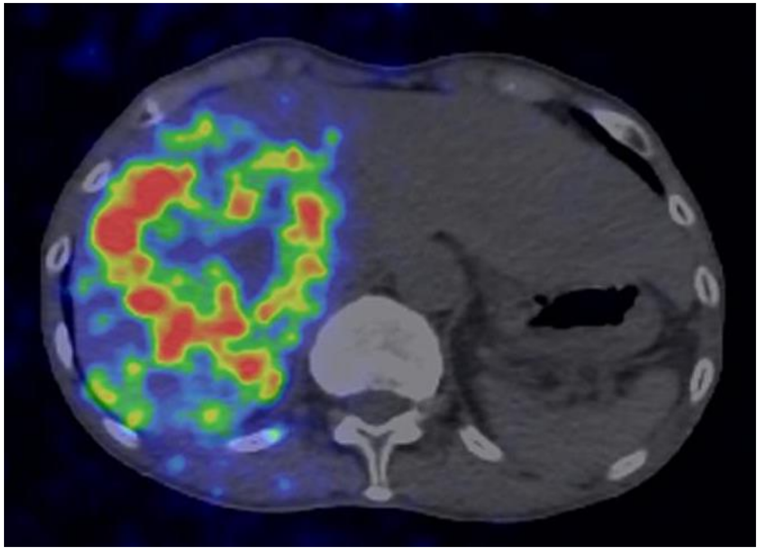


PET imaging from Y90

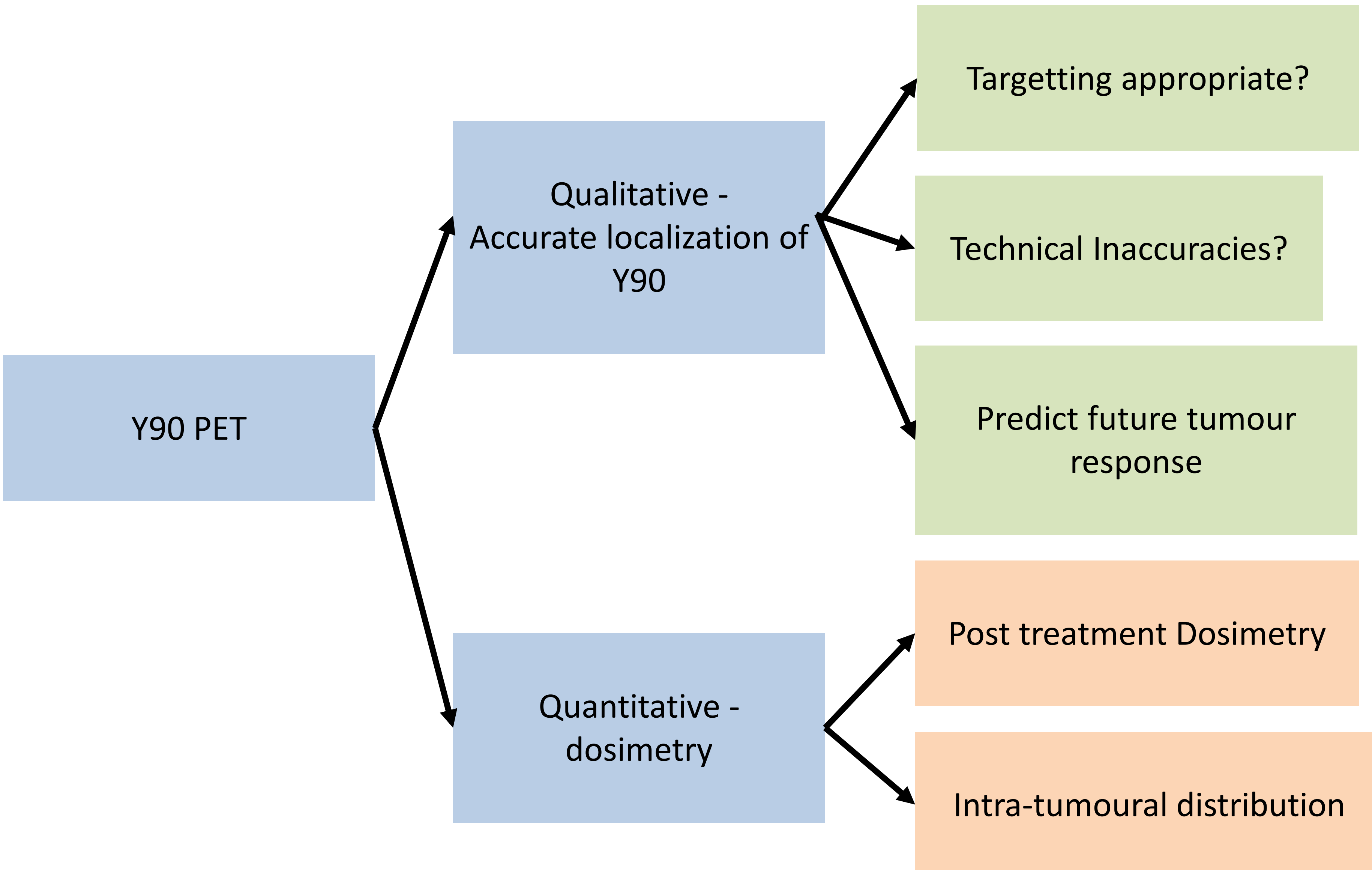
- **GOOD POINTS**
1. Better resolution than bremsstrahlung
2. co-incident gamma photons corrected for attenuation
3. Potential for quantification – and actual absorbed dose calculation
4. Much higher pixel resolution

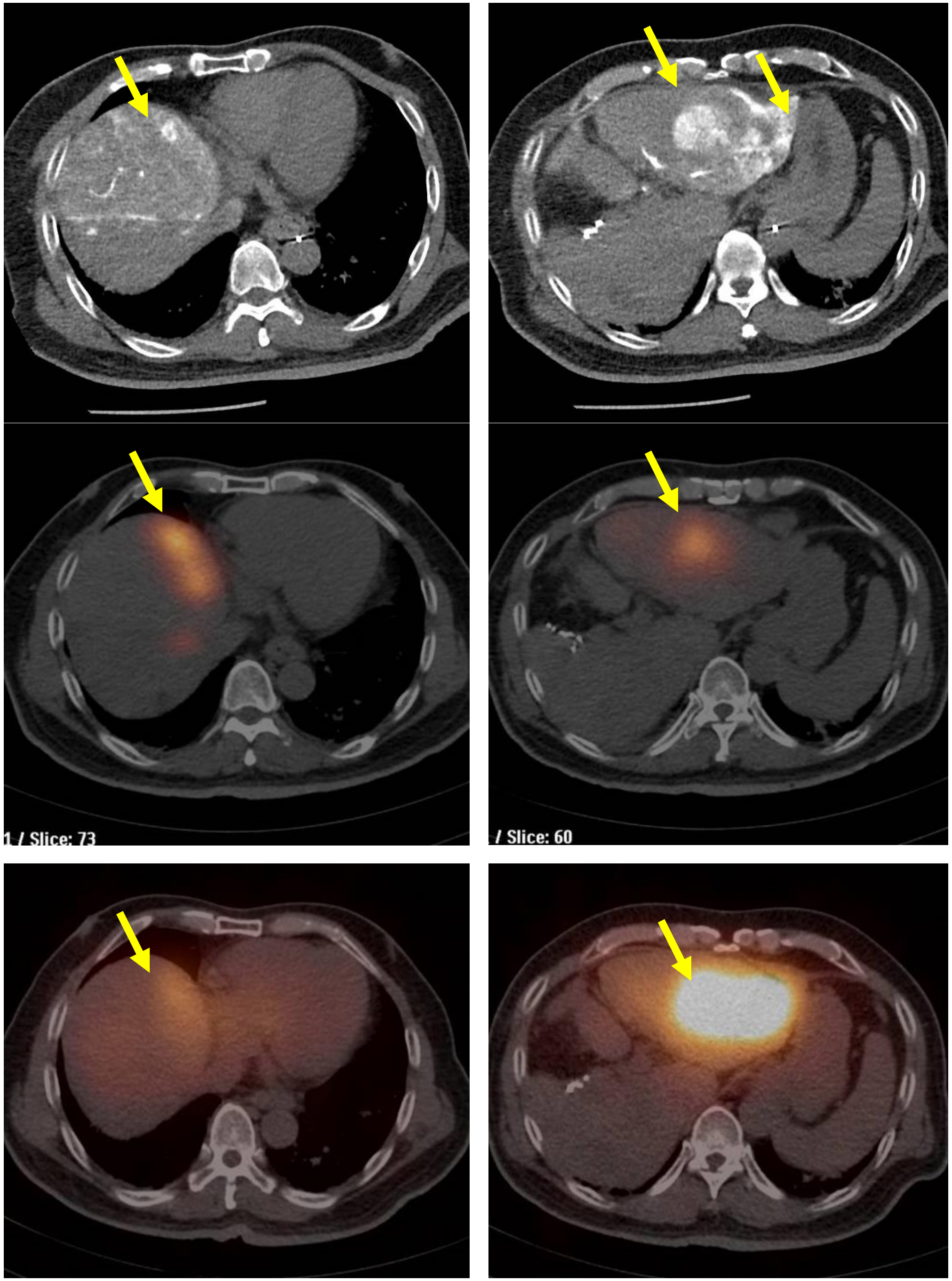


- **BAD POINTS**
1. 32 ppm internal pair production = Small amount of positron emission
2. Poor counts rate, poor signal-to-noise ratio (SNR)
3. Long acquisition time (typically 30 mins per bed position for average activity of Y90)



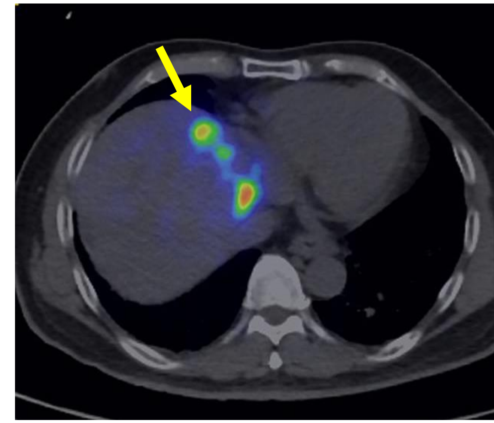
So is Y90 PET useful?



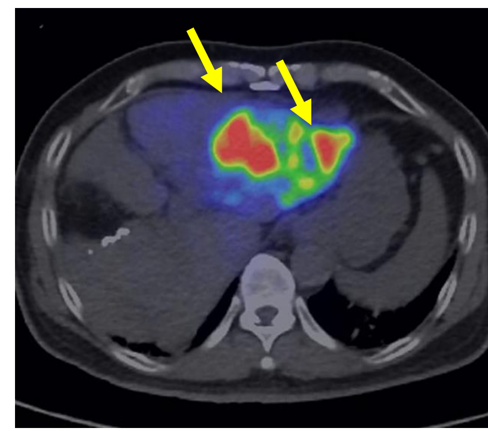


Accuracy in targeting

Hepatic CT angiography



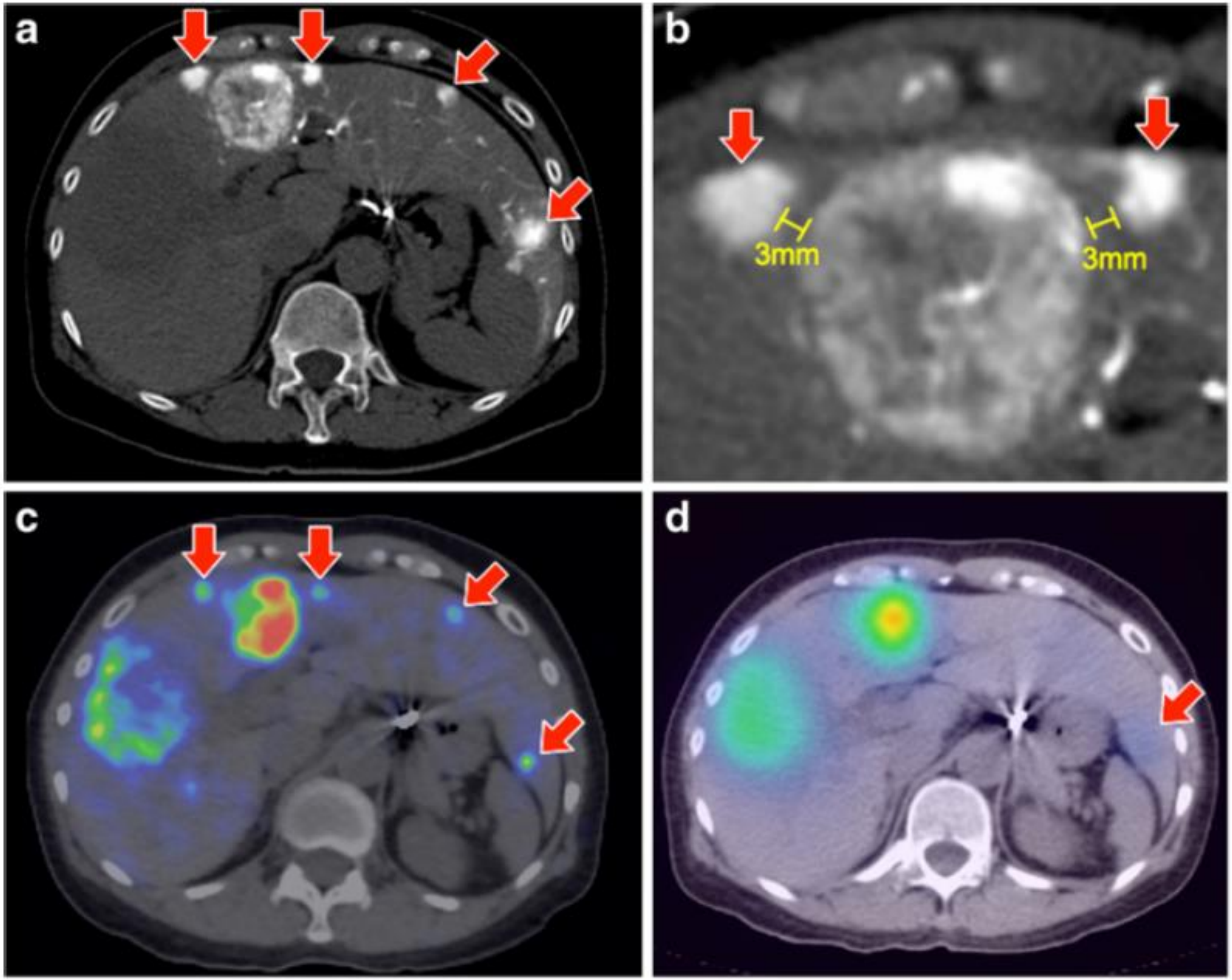
MAA
SPECTCT



Y90 PETCT

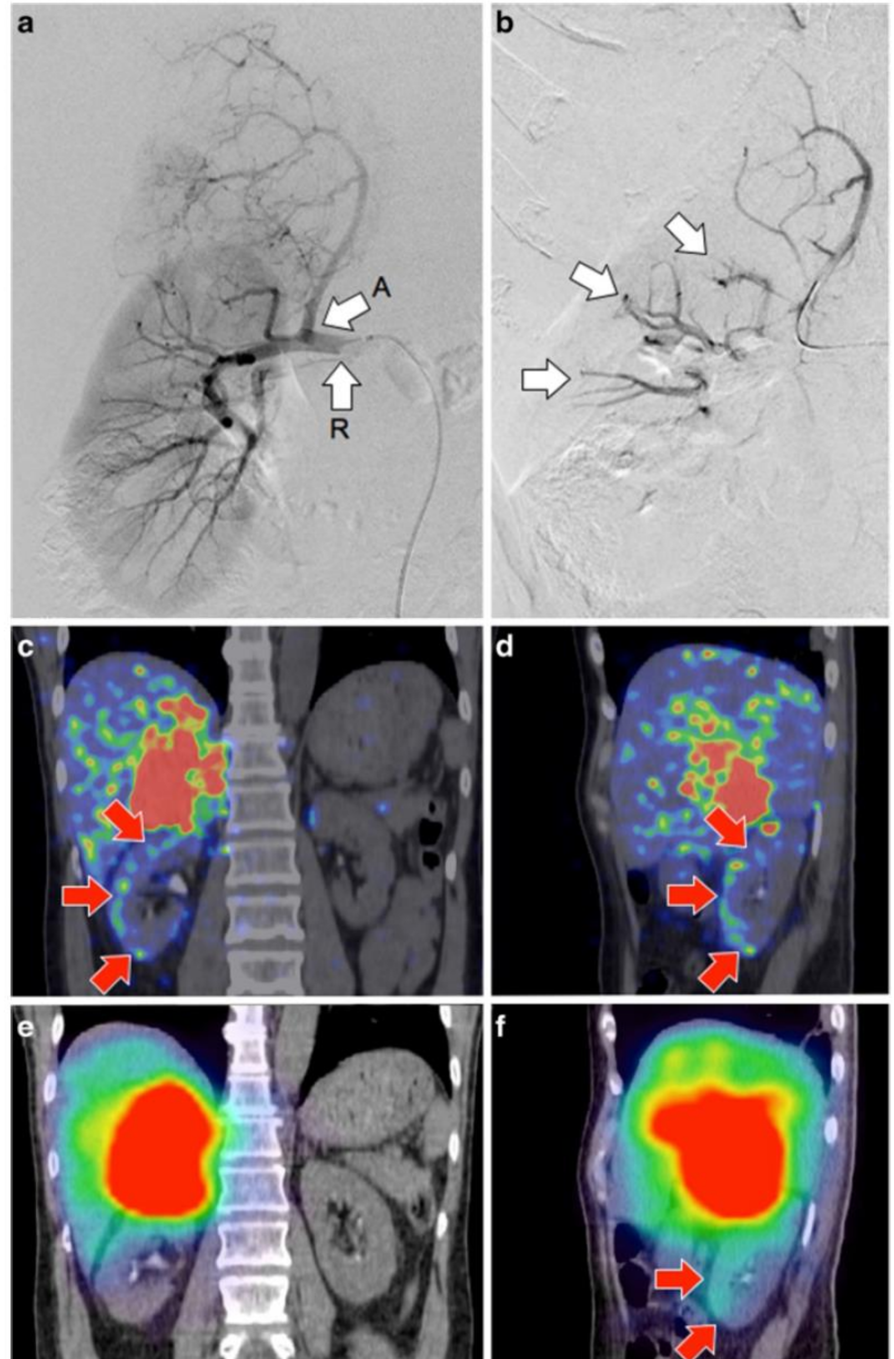
Small lesions are identified by PET.

Bremstrahlung


a
b
3mm
3mm
c
d

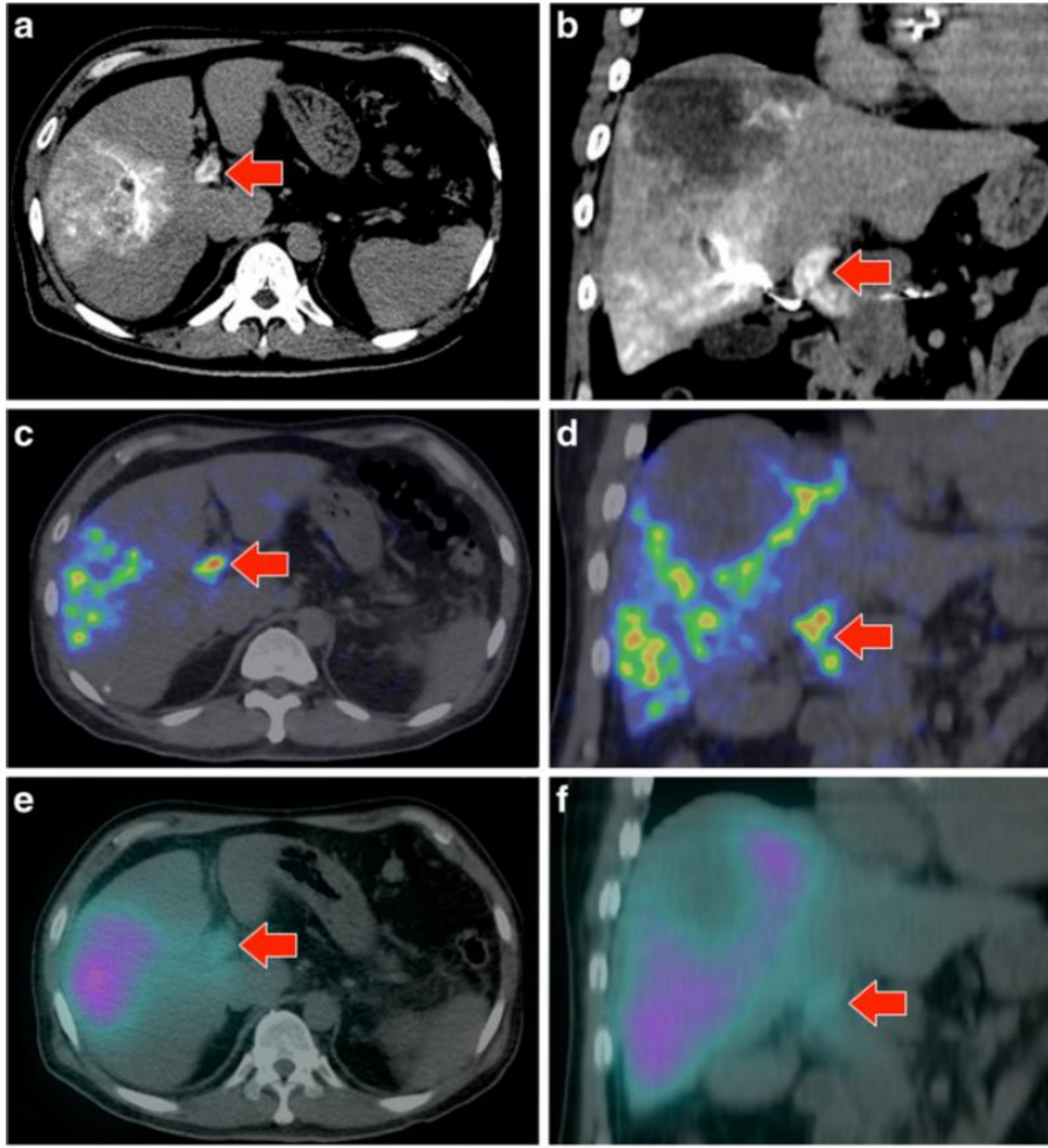
Evaluating Technical Inaccuracies

- Supply to HCC from a branch from the right renal artery.
- Post-Y90 infusion, there is some microspheres reflux seen in the right renal cortex (visible only on PET)



Predicting future response

- Better localization of microspheres.
- Allows for better prediction of future response or treatment failure.
- Portal vein tumour thrombus localized by Y90 PET but not by bremsstrauhlung SPECTCT



Quantitative?
Y90 PET/CT for post-Y90 dosimetry

Due to the better resolution of Y90 PET and attenuation correction, quantitative analysis can be performed for absorbed dosimetry.

<u>2 methods of doing PET-based post-treatment dosimetry</u>:

(1) Count-based with reference to a standard activity

- (Kao Y H et al, see next few slides)

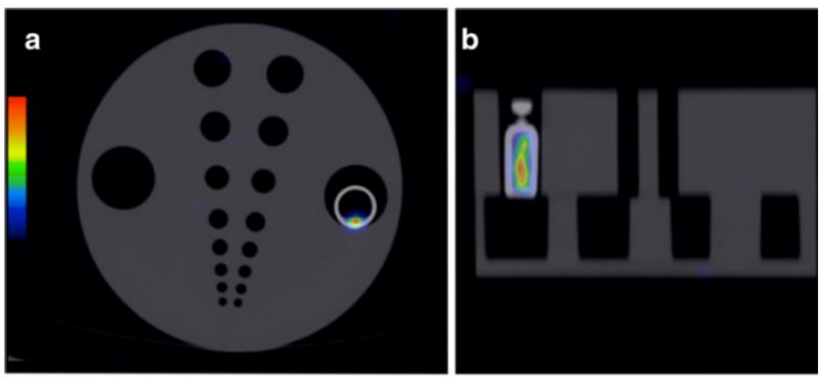
(2) Count-based with image convolution with Y90 voxel dose-kernel (Monte Carlo or derived)

- (Ng S C et al, see next few slides)

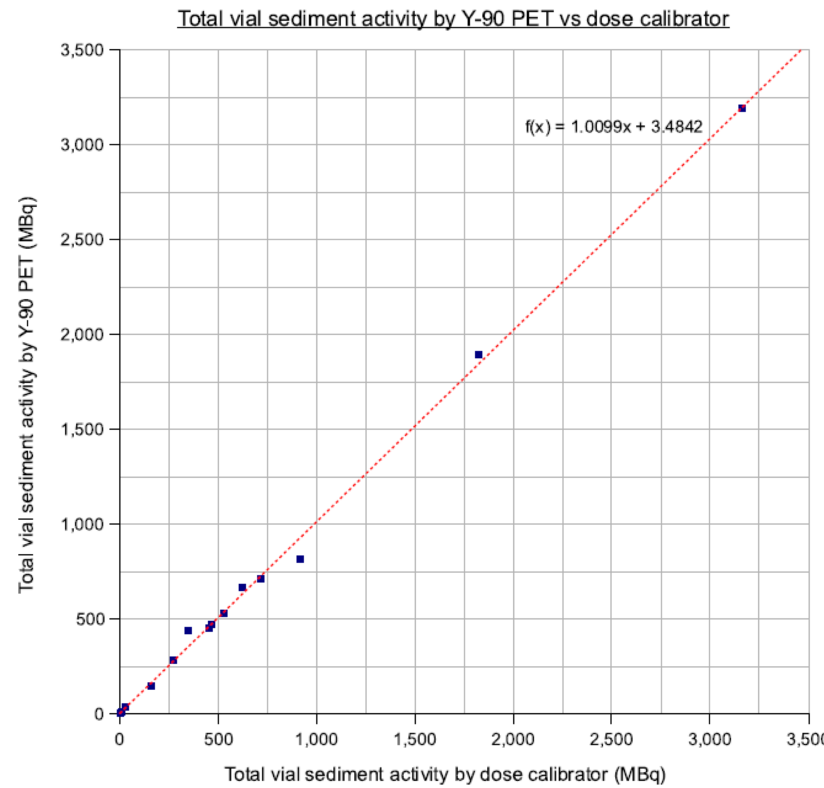
(I) Using Y90 PET/CT for post-Y90 dosimetry

Post-radioembolization yttrium-90 PET/CT - part 2: dose-response and tumor predictive dosimetry for resin microspheres

Yung-Hsiang Kao[1,2,3]*, Jeffrey D Steinberg[4], Young-Soon Tay[1], Gabriel KY Lim[1], Jianhua Yan[5], David W Townsend[5], Charley A Budgeon[6,7], Jan A Boucek[2], Roslyn J Francis[2,13], Timothy ST Cheo[8], Mark C Burgmans[9,14], Farah G Irani[9], Richard HG Lo[9], Kiang-Hiong Tay[9], Bien-Soo Tan[9], Pierce KH Chow[10,11,12], Somanesan Satchithananthan[1], Andrew EH Tan[1], David CE Ng[1] and Anthony SW Goh[1]

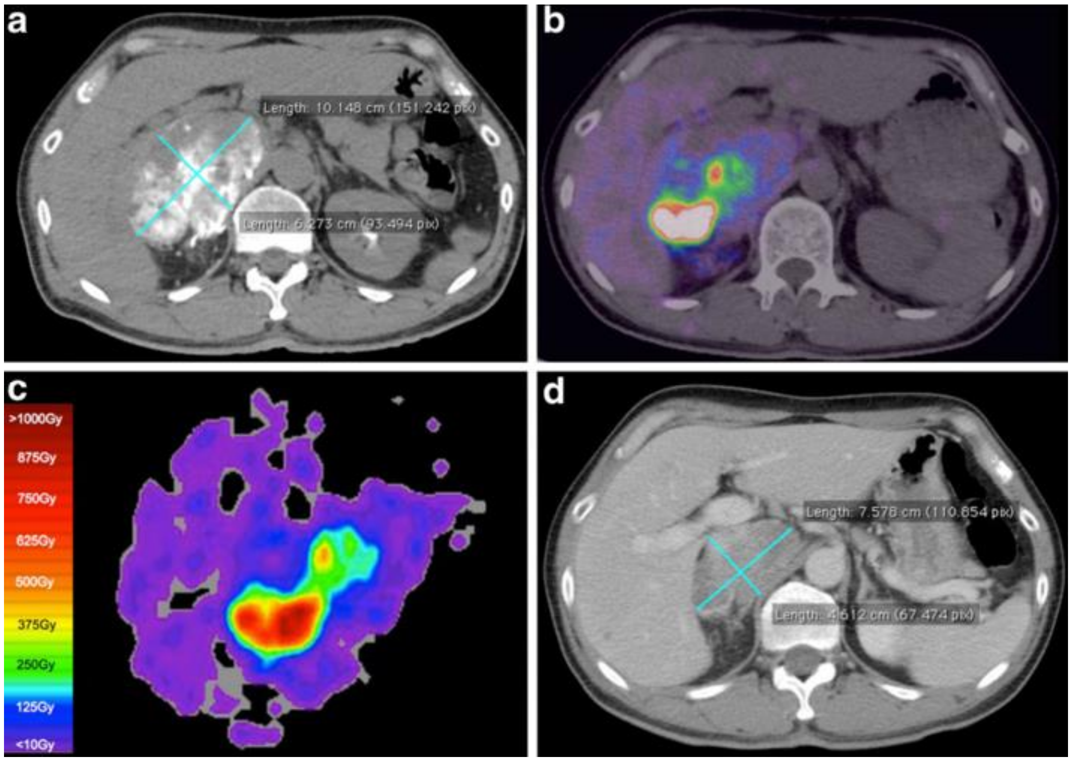


- Standard vial Y90 activity imaged
- Shows a linear correlation with vial activity measured in dose calibrator
- Counts are directly correlated to dose activity



Kao *et al. EJNMMI Research* 2013, **3**:57

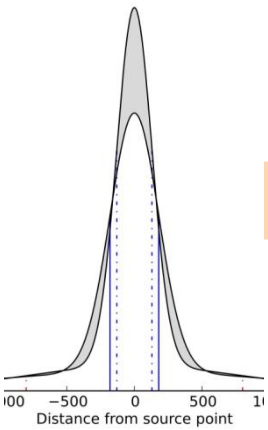
(I) Using Y90 PET/CT for post-Y90 dosimetry

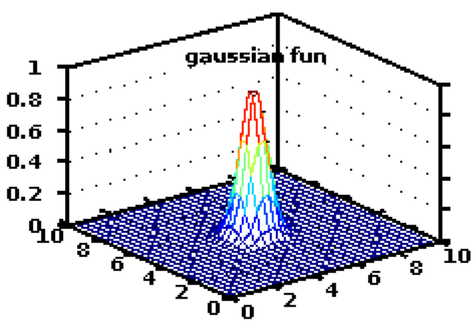


- Voxel counts are obtained from the PET image
- Decay-corrected counts
- Voxel volume and lesional volume obtained
- Radioactivity is estimated through standard source and linearity of counts/MBq
- Based on 50Gy kg per GBq of energy deposited, using the radioactivity and lesional volume, the absorbed dose can be calculated

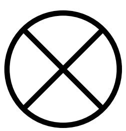
(II) Using Y90 PET/CT for post-Y90 dosimetry

Point source Y90 beta energy dose-kernel or pdf

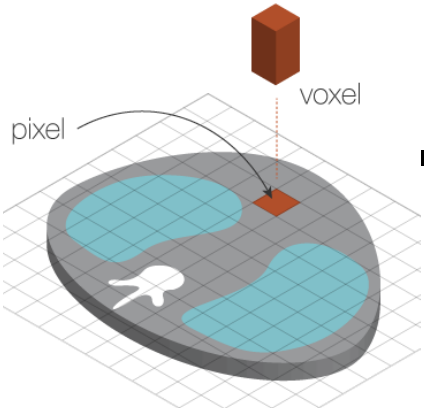


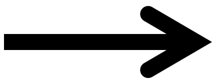


convolution

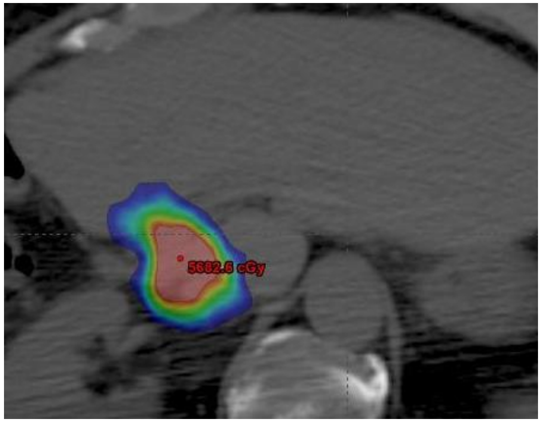


Pixel/voxel intensity/counts





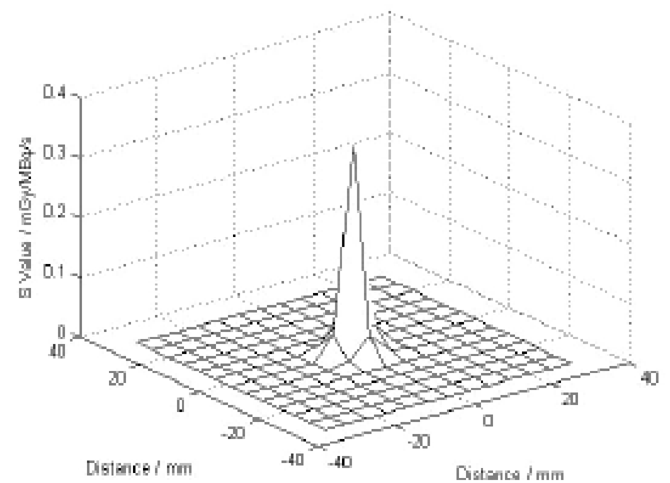
Summed over all pixels = absorbed dose to tumour

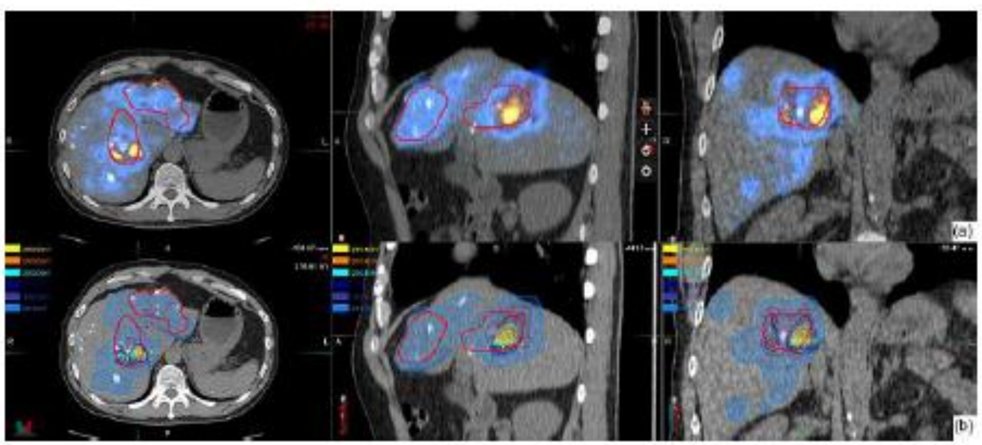


Patient dosimetry for ^{90}Y selective internal radiation treatment based on ^{90}Y PET imaging

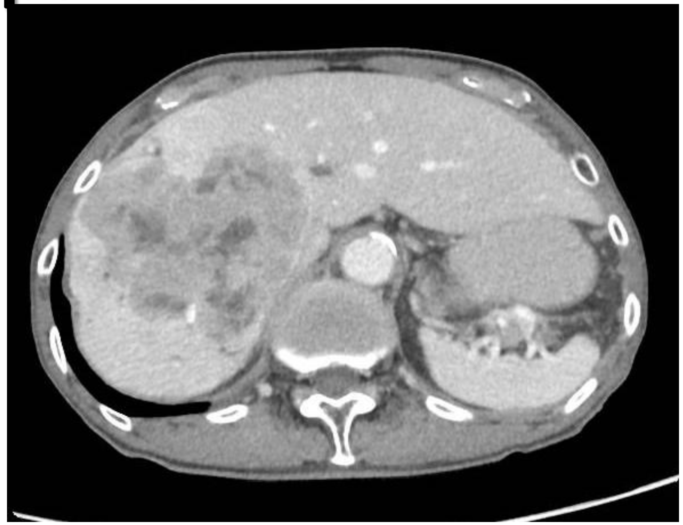
Sherry C. Ng,[1a] Victor H. Lee,[2] Martin W. Law,[3] Rico K. Liu,[1]
Vivian W. Ma,[3] Wai Kuen Tso,[3] To Wai Leung[1]
Department of Clinical Oncology,[1] Queen Mary Hospital, Hong Kong; Department of Clinical Oncology,[2] University of Hong Kong, Hong Kong; Department of Diagnostic Radiology,[3] Queen Mary Hospital, Hong Kong
ngchoryi@yahoo.com

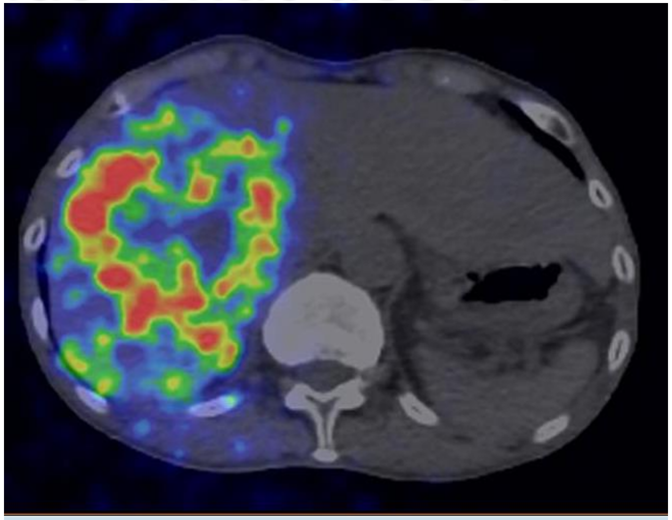
In this method, Y90 PET images were convolved with a Monte Carlo generated voxel dose kernel to obtain the dose to tumour and non-tumour tissues in 5 patients.





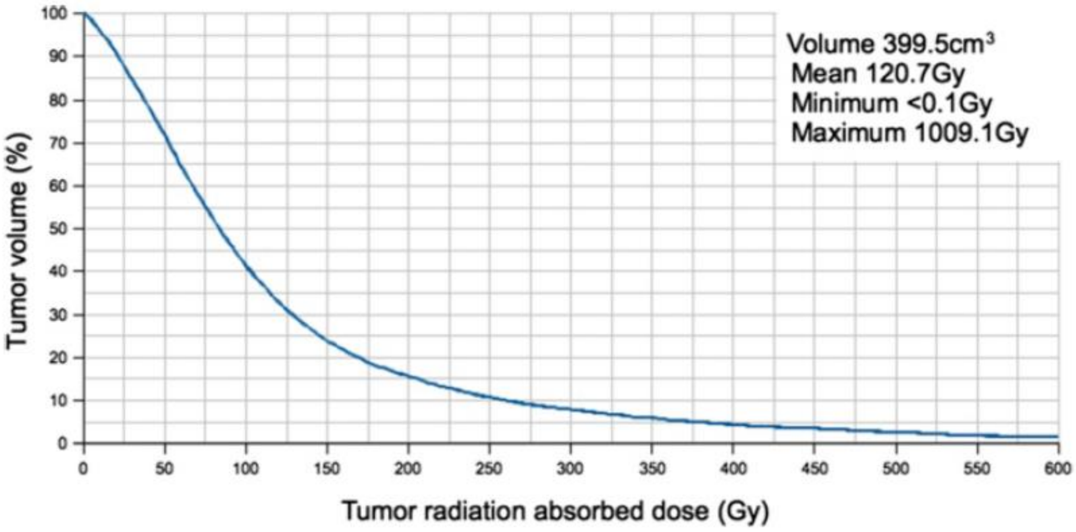
(III) Imaging intra-tumoural distribution: which part of the tumour has what dose?





In addition to whole tumour dosimetry, internal intra-tumoural dosimetry due to tumour heterogeneity can be obtained.

- Obtain the Dose-Volume histogram
- ie. how much volume of the tumour has received what cumulative dose?



Recommendations for optimizing Y90 PET/CT for post-Y90 dosimetry

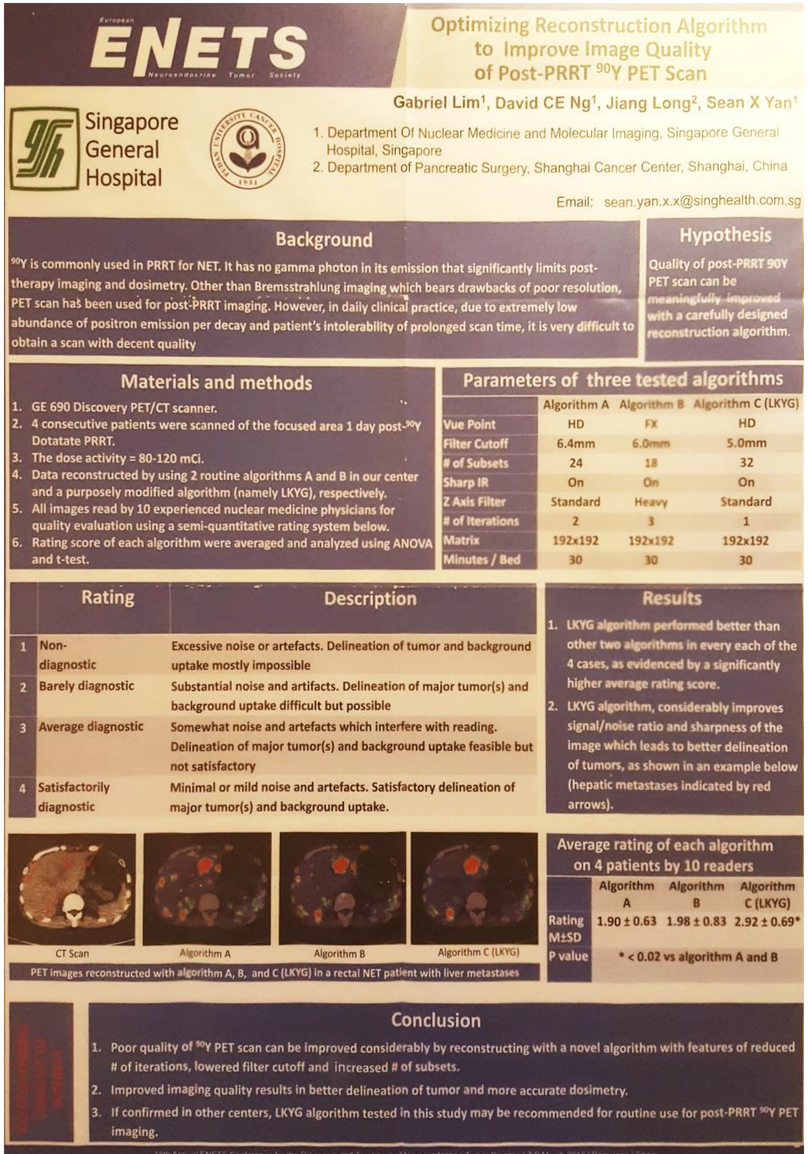
Recommendations

1. Time-of-flight (TOF) – improve signal-to-noise ratio and resolution
2. Iterative reconstruction – fewer iterations
3. Intrinsic noise from LSO crystals, some use BGO
4. Longer time of acquisition 20-30 mins/bed position

Josep M Marti-Climent, et al. PET Optimization for improved assessment and accurate quantification of 90Y-microsphere biodistribution after radioembolization
Med Phys 2014; 41: 092503

Carlier T, et al, (90)Y -PET imaging: Exploring limitations and accuracy under conditions of low counts and high random fraction. Med Phys 2015; 42:4295-309

Y90 PET reconstruction DNMMI



European ENETS Neuroendocrine Tumor Society

Optimizing Reconstruction Algorithm to Improve Image Quality of Post-PRRT ^{90}Y PET Scan

Gabriel Lim[1], David CE Ng[1], Jiang Long[2], Sean X Yan[1]

Singapore General Hospital

1. Department Of Nuclear Medicine and Molecular Imaging, Singapore General Hospital, Singapore
2. Department of Pancreatic Surgery, Shanghai Cancer Center, Shanghai, China

Email: sean.yan.x.x@singhealth.com.sg

Background

^{90}Y is commonly used in PRRT for NET. It has no gamma photon in its emission that significantly limits post-therapy imaging and dosimetry. Other than Bremsstrahlung imaging which bears drawbacks of poor resolution, PET scan has been used for post-PRRT imaging. However, in daily clinical practice, due to extremely low abundance of positron emission per decay and patient's intolerability of prolonged scan time, it is very difficult to obtain a scan with decent quality

Hypothesis

Quality of post-PRRT 90Y PET scan can be meaningfully improved with a carefully designed reconstruction algorithm.

Materials and methods

1. GE 690 Discovery PET/CT scanner.
2. 4 consecutive patients were scanned of the focused area 1 day post-^{90}Y Dotatate PRRT.
3. The dose activity = 80-120 mCi.
4. Data reconstructed by using 2 routine algorithms A and B in our center and a purposely modified algorithm (namely LKYG), respectively.
5. All images read by 10 experienced nuclear medicine physicians for quality evaluation using a semi-quantitative rating system below.
6. Rating score of each algorithm were averaged and analyzed using ANOVA and t-test.

Parameters of three tested algorithms

	Algorithm A	Algorithm B	Algorithm C (LKYG)
Vue Point	HD	FX	HD
Filter Cutoff	6.4mm	6.0mm	5.0mm
# of Subsets	24	18	32
Sharp IR	On	On	On
Z Axis Filter	Standard	Heavy	Standard
# of Iterations	2	3	1
Matrix	192x192	192x192	192x192
Minutes / Bed	30	30	30

	Rating	Description
1	Non-diagnostic	Excessive noise or artefacts. Delineation of tumor and background uptake mostly impossible
2	Barely diagnostic	Substantial noise and artifacts. Delineation of major tumor(s) and background uptake difficult but possible
3	Average diagnostic	Somewhat noise and artefacts which interfere with reading. Delineation of major tumor(s) and background uptake feasible but not satisfactory
4	Satisfactorily diagnostic	Minimal or mild noise and artefacts. Satisfactory delineation of major tumor(s) and background uptake.

Results

1. LKYG algorithm performed better than other two algorithms in every each of the 4 cases, as evidenced by a significantly higher average rating score.
2. LKYG algorithm, considerably improves signal/noise ratio and sharpness of the image which leads to better delineation of tumors, as shown in an example below (hepatic metastases indicated by red arrows).

CT Scan | Algorithm A | Algorithm B | Algorithm C (LKYG)

PET images reconstructed with algorithm A, B, and C (LKYG) in a rectal NET patient with liver metastases

Average rating of each algorithm on 4 patients by 10 readers

	Algorithm A	Algorithm B	Algorithm C (LKYG)
Rating M±SD	1.90 ± 0.63	1.98 ± 0.83	2.92 ± 0.69*
P value	* < 0.02 vs algorithm A and B		

Conclusion

1. Poor quality of ^{90}Y PET scan can be improved considerably by reconstructing with a novel algorithm with features of reduced # of iterations, lowered filter cutoff and increased # of subsets.
2. Improved imaging quality results in better delineation of tumor and more accurate dosimetry.
3. If confirmed in other centers, LKYG algorithm tested in this study may be recommended for routine use for post-PRRT ^{90}Y PET imaging.

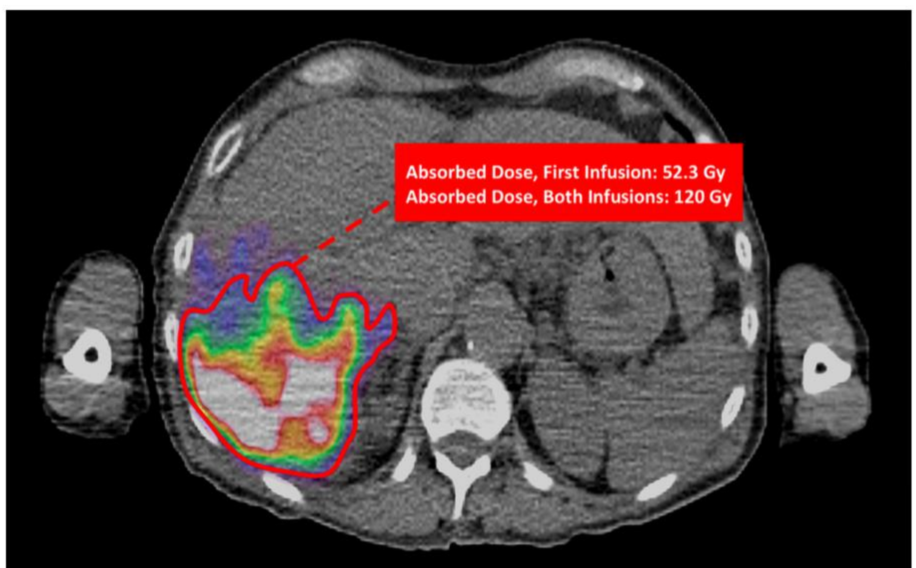
- Recon Method: VUE Point HD
- Filter Cutoff (mm): 5 mm.
- Z axis Filter : Standard.
- Subsets: 32.
- Iterations: 1.
- Matrix: 192 x 192.
- 30 minutes/Bed position

Intraprocedural Yttrium-90 Positron Emission Tomography/CT for Treatment Optimization of Yttrium-90 Radioembolization

Austin C. Bourgeois, MD, Ted T. Chang, MD, Yong C. Bradley, MD, Shelley N. Acuff, CNMT, and Alexander S. Pasciak, PhD

ABSTRACT

Radioembolization with yttrium-90 (^{90}Y) microspheres relies on delivery of appropriate treatment activity to ensure patient safety and optimize treatment efficacy. We report a case in which ^{90}Y positron emission tomography (PET)/computed tomography (CT) was performed to optimize treatment planning during a same-day, three-part treatment session. This treatment consisted of (*i*) an initial ^{90}Y infusion with a dosage determined using an empiric treatment planning model, (*ii*) quantitative ^{90}Y PET/CT imaging, and (*iii*) a secondary infusion with treatment planning based on quantitative imaging data with the goal of delivering a specific total tumor absorbed dose.



JVIR 2014; 25: 271-5

Summary

1. Y90 PET is clinically useful in certain situations.
2. Qualitatively, it allows for more precise localization/targetting, identification of technical inaccuracies, predicting of future response
3. Quantitatively, it allows for post treatment dosimetry to determine accurate absorbed dose and to estimate intra-tumoural absorbed doses due to tumour heterogeneity, facilitating prediction of response of tumour.
4. Improvement of PET imaging techniques/application to dosimetry is still in progress. There is still much to do.

Acknowledgements

I would like to thank the people who have worked to produce the results shown in this presentation:

- Dr Kao Yung Hsiang, Dr Sean Yan, Gabriel Lim and doctors, Nuclear Medicine technologists, laboratory staff, medical physicists in the department of Nuclear Medicine and Molecular Imaging, Singapore General Hospital
- Scientists at the Clinical Imaging Research Centre (CIRC), NUS
- Interventional Radiologists

Thank you for your attention

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