J of Nuclear Medicine Technology, first published online April 19, 2022 as doi:10.2967/jnmt.121.263422

BRIEF COMMUNICATIONS

TITLE

Indirect lung absorbed dose verification by yttrium-90 PET/CT and complete lung protection by hepatic vein balloon occlusion: proof-of-concept

AUTHORS

Yung Hsiang Kao[1], Calvin Gan[2], Alicia Corlett[1], Alexander Rhodes[2], Dinesh Sivaratnam[1], Beng Ghee Lim[2]

[1] Department of Nuclear Medicine, Royal Melbourne Hospital, Parkville, Victoria, Australia
[2] Department of Radiology, Royal Melbourne Hospital, Parkville, Victoria, Australia

KEYWORDS

Radioembolization, selective internal radiation therapy, lung shunt fraction, yttrium-90 PET/CT, hepatic vein balloon occlusion

ABSTRACT

Post-radioembolization lung absorbed dose verification was historically problematic and impractical in clinical practice. We devised an indirect method using yttrium-90 PET/CT. Conceptually, true lung activity is simply the difference between the total prepared activity minus all activity below the diaphragm and residual activity within delivery apparatus. Patient-specific lung mass is measured by CT densitovolumetry. True lung mean absorbed dose is calculated by MIRD macrodosimetry. Proof-of-concept is shown in a hepatocellular carcinoma patient with high lung shunt fraction 26%, where evidence of technically successful hepatic vein balloon occlusion for radioembolization lung protection was required. Indirect lung activity quantification showed the post-radioembolization lung shunt fraction to be reduced to approximately 1% with true lung mean absorbed dose approximately 1Gy, suggesting complete lung protection by hepatic vein balloon occlusion. We discuss possible clinical applications such as lung absorbed dose verification, refining the limits of lung tolerance and the concept of massive activity radioembolization.

Abstract word count: 150 words

MANUSCRIPT

INTRODUCTION

Despite decades of radioembolization, the true tolerance limit of the lung to radioembolization has not yet been properly defined and to date, has only been *estimated* by technetium-99m macroaggregate albumin (99mTc MAA) or extrapolated from the experiences of external beam radiotherapy (*1*). This problem is compounded by different methods of imaging and calculating the lung shunt fraction, lung mass and radiobiologically distinct microsphere devices (*1*).

In the past decade, yttrium-90 positron emission tomography with contemporaneous computed tomography (90Y PET/CT) has rapidly evolved to become the current standard of care in post-radioembolization verification of tumour and non-tumorous liver absorbed doses and detection of non-target abdominal activity (*2-3*). However, direct lung 90Y PET/CT is much more problematic. Firstly, lung radioconcentration within a PET field-of-view is usually low because the prescribed lung mean absorbed dose is limited to <20-25Gy, resulting in noisy, quantitatively inaccurate lung scans (*1-2,4*). Secondly, increasing lung scan time to improve count statistics is impractical. Abdominal 90Y PET/CT of 1 to 2 bed positions requires 20 to 40 minutes. Doubling lung scan time over 2 bed positions could take 40 to 80 minutes just for lungs alone, intolerable for any patient. Thirdly, dedicating 60 to 120 minutes of scanner time for a single patient costs the throughput equivalent of approximately 3 to 6 oncology PET patients which is difficult to justify financially.

MATERIALS AND METHODS

Dosimetric concept

Conceptually, the true lung activity is simply the difference between the total prepared activity minus all activity below the diaphragm and residual activity within the delivery apparatus (*5*). Expressed as an equation, where radiomicrospheres are permanent implants within a closed system where all injected activity is conserved and activity leeching is negligible:

$$A_{Total} = A_{Lung} + A_{PTV} + A_{Non\text{-}target} + A_{Residual}$$

i.e. $$A_{Lung} = A_{Total} - (A_{PTV} + A_{Non\text{-}target} + A_{Residual})$$

Where A_{Total} is total prepared activity, A_{Lung} is lung activity, A_{PTV} is activity within all Planning Target Volumes, $A_{Non\text{-}target}$ is abdominal non-target activity (if any), and $A_{Residual}$ is residual activity within delivery apparatus. The term “Planning Target Volume” refers to all targeted arterial territories encompassing tumour and non-tumorous liver (*6*). All measured activities are decay corrected to the time of radioembolization. The lung mean absorbed dose is calculated by Medical Internal Radiation Dose (MIRD) macrodosimetry assuming uniform activity biodistribution, using 90Y absorbed dose coefficient 50Gy per GBq/kg (*2,6*):

$$D_{Lung} = 50 \times (A_{Lung} / M_{Lung})$$

Where D_{Lung} is true lung mean absorbed dose (Gy), A_{Lung} is lung activity (GBq) and M_{Lung} is patient-specific lung mass (kg) measured by CT densitovolumetry (*7*).

Clinical proof-of-concept

We demonstrate this concept in a hepatocellular carcinoma patient with high lung shunt fraction, where we implemented lung protection during radioembolization by hepatic vein balloon occlusion but required objective proof of technical success. This was eventually proven by the indirect method described here. We considered lung protection to be “complete” if the extent of hepatopulmonary shunting was reduced to a clinically negligible level i.e., approximately 1%. This report has been approved by the institutional review board. The patient consented to the radioembolization planning, treatment and this publication.

An 82-year-old man with large inoperable 12cm hepatocellular carcinoma occupying segments 4 and 8 (Fig. 1A) was referred for 90Y resin microsphere radioembolization (SIR-Spheres, Sirtex Medical Limited, Australia). Exploratory hepatic angiography with radiomicrosphere simulation confirmed hypervascularity with good tumoral 99mTc MAA implantation. However, planar liver-lung scintigraphy showed a high lung shunt of 26% (Fig. 1B). We proceeded with radioembolization by implementing two methods of lung protection. Firstly,

activity prescription was limited to lung safety tolerance of 20Gy, planned by MIRD method (i.e., Partition Model) (*4,6*). Secondly, hepatic vein occlusion of the right and middle hepatic veins was performed prior to radiomicrosphere infusion to minimize hepatopulmonary shunting; this has the additional benefit of improving the tumour mean absorbed dose by retaining radiomicrospheres within tumour instead of being shunted to the lung (*8*).

For hepatic vein balloon occlusion, LeMaitre 6F Over-The-Wire Embolectomy Catheters (LeMaitre Vascular, USA) were placed in the right and middle hepatic veins (catheter length 80cm; 0.035-inch guidewire) under fluoroscopic guidance via the right internal jugular vein (*8*). Balloons were inflated prior to radiomicrosphere infusion, with complete occlusion of the right and middle hepatic veins visually confirmed with contrast injection (Fig. 1C). Total balloon inflation time approximately was 20 minutes during radioembolisation (Fig. 1D). Despite visual confirmation of balloon occlusion, there remains the possibility of an unknown and invisible amount of in-transit venous radiomicrospheres temporarily suspended proximal to the inflated balloons, potential for radiomicrosphere dislodgement from tumour into the lungs after balloon deflation, and unknown lung shunt contribution by the patent left hepatic vein. All of these uncertainties require post-radioembolization confirmation of the true lung activity to assure patient safety.

Post-radioembolisation bremsstrahlung planar imaging did not show any visually significant lung activity, a qualitative indication of successful lung protection (Fig. 2A). 90Y PET/CT of the abdomen and delivery apparatus (including catheters, occlusion balloons, drapes) were separately performed as a gradual sweep over 20 min to image the whole liver and delivery apparatus (*2,5*). Our PET/CT scanner is the Biograph Horizon (Siemens, Erlangen, Germany). 90Y PET images were reconstructed using Siemens TrueX time-of-flight iterative algorithm, 3 iterations and 10 subsets, gaussian filter 5mm full width half maximum and 180x180 matrix. Low-dose CT was performed for localization, attenuation correction, and scatter correction. Images were displayed in 3mm slice thickness and analyzed using Siemens SyngoVia software.

RESULTS

A_{PTV} was quantified by a large volume-of-interest encompassing all Planning Target Volumes, setting the PET isocontour threshold to 2% by visual assessment to obtain 1.234GBq, after decay correction (Fig. 2B). A few small foci of noise artifacts were deemed negligible. $A_{Residual}$ in delivery apparatus was similarly quantified by setting the PET isocontour threshold to 1% (Fig.2C) to obtain 0.015GBq, after decay correction (*5*). $A_{Non\text{-}target}$ was undetectable, taken to be zero. A_{Total} was 1.266GBq measured by dose calibrator during radiomicrosphere v-vial preparation, after decay correction.

A_{Lung} is therefore 1.266 - (1.234 + 0.015) = 0.017GBq. Accounting for $A_{Residual}$, the true lung shunt fraction is therefore (0.017 / 1.266) x 100 = approximately 1%. This result was consistent with qualitative bremsstrahlung lung findings and was a vast improvement from the original 26%, objectively affirming technically success and complete lung protection by hepatic vein balloon occlusion. His lung mass was measured by CT densitovolumetry to be 0.85kg (*7*). D_{Lung} is therefore 50 x (0.017 / 0.85) = approximately 1Gy. Clinically, the patient did not develop any respiratory symptoms and follow-up MRI scan two months later did not show any evidence of pneumonitis on the routinely acquired high resolution GRE T1 and HASTE T2 sequences, clinically validating our lung protection methods and calculations. Hepatic vein balloon occlusion had also improved the tumour mean absorbed dose from an initial 88Gy simulated by 99mTc MAA predictive dosimetry, to final 101Gy verified by 90Y PET/CT (Fig. 2D) (*6*). Four-month follow-up MRI showed a mild size reduction of the tumour mass, clinically consistent with the 90Y PET/CT absorbed dose verification.

DISCUSSION

This technical report demonstrates two concepts: firstly, the true lung absorbed dose may be indirectly quantified by 90Y PET/CT; secondly, complete lung protection by hepatic vein balloon occlusion is possible. A recent comprehensive review by Kappadath et al. highlighted the historical pitfalls and limitations in our current methods of lung radiation planning for radioembolization (*1*). This is attributable to a lack of standardized methods for calculating the lung shunt fraction, lung dosimetry and our incomplete radiobiologic understanding of the true lung tolerance to radiomicrospheres (*1*). Furthermore, our current understanding of approximately 20-25Gy lung tolerance for 90Y resin microspheres is not wholly applicable to 90Y glass microspheres due to differences in specific activity and tissue biodistribution. As we gradually gain clarity on the true limits of lung tolerance, we will further improve lung predictive dosimetry by utilizing Normal Tissue Complication Probability (*4*).

In clinical practice, accurate lung dosimetry is important for both pre-radioembolization predictive dosimetry and also post-radioembolization absorbed dose verification. During pre-radioembolization predictive dosimetry, a common strategy to overcome tumour absorbed dose heterogeneity is to deliberately escalate the prescribed activity up to the limits of normal tissue safety tolerance (*9*). The lung is often the activity limiting critical organ and therefore clear knowledge of the true lung tolerance limit is vital to avoid significant radiomicrosphere pneumonitis (*4*). Our method of indirect lung absorbed dose verification could enable us to describe the true lung shunt fraction of different tumour types and establish the true limits of lung tolerance for radiobiologically distinct radiomicrosphere devices.

After radioembolization, lung absorbed dose verification may be clinically important depending on the treatment strategy. Our case of lung protection by hepatic vein balloon occlusion proved to be technically successful, therefore no further action was required. However, if the lung absorbed dose was unexpectedly found to be dangerously high, immediate action can be initiated to mitigate the risk of developing severe pneumonitis in the ensuing weeks. Such mitigative measures may include corticosteroids, respiratory advice and close outpatient respiratory surveillance in the weeks after radioembolization.

Hepatic vein balloon occlusion is an established technique that may be deployed in situations of high lung shunting (*8*). However, objective proof of technically successful hepatic vein balloon occlusion expressed in terms of a measured absolute reduction in lung activity, lung shunt fraction or lung absorbed dose has not been described. This report shows that complete lung protection is possible by hepatic vein balloon occlusion. This means that nearly all injected radiomicrospheres can be retained within the liver to maximize the tumour absorbed dose and avoid unnecessary lung irradiation. This is especially important for hepatocellular carcinoma where the lung shunt fraction is typically higher than liver metastases, which may preclude safe nor effective radioembolization. Complete lung protection renders the lung shunt fraction less relevant, allowing massive activities to be infused for radiomicrosphere lobectomy or segmentectomy. With complete lung protection, repeated radioembolization would also be safer because the cumulative lung absorbed dose would be low.

The main dosimetric limitation of our method of indirect quantification is that it can only obtain the true lung *mean* absorbed dose, to be superseded in the future by lung dose-volume histograms (*4, 9*). However, the true lung dose-volume histogram will remain elusive until 90Y PET/CT further improves in acquisition speed, field-of-view (e.g., “total body” PET scanners) and quantitative accuracy to permit direct lung imaging in the routine clinical setting. There were also several technical assumptions in this work. Firstly, we assumed 90Y PET to be quantitatively accurate. Secondly, we assumed that our visual method of PET isocontour thresholding was reliable to encompass all true 90Y activity, and that all excluded activity was negligible. Thirdly, we assumed that background noise artifacts had negligible effect on clinical dosimetry. However, we felt that these assumptions were reasonable given our prior validation work and years of experience with 90Y PET (*2-3*, *5*).

CONCLUSION

Indirect lung absorbed dose verification by 90Y PET/CT is feasible and could improve clinical management and our knowledge of lung safety thresholds. Complete lung protection by hepatic vein balloon occlusion is possible, suggesting a new paradigm where the lung shunt fraction is less relevant and permits massive activity radioembolization for radiomicrosphere lobectomy or segmentectomy. Further research is needed to explore these new concepts.

KEY POINTS

QUESTION

How do we verify the true lung absorbed dose after radioembolization?

PERTINENT FINDINGS

We devised a simple method to indirectly calculate the true lung absorbed dose using post-radioembolization 90Y PET/CT. By this method, we showed that hepatic vein balloon occlusion could achieve complete lung protection from hepatopulmonary shunting of radiomicrospheres.

IMPLICATIONS FOR PATIENT CARE

Post-radioembolization indirect lung absorbed dose verification is feasible and may benefit patients in terms of mitigating lung radiotoxicity, safety of repeated radioembolization and research to better define the true limits of lung radiomicrosphere tolerance. By proving that complete lung protection was possible using hepatic vein balloon occlusion, we suggest a possible new paradigm of massive activity radioembolization to benefit radiomicrosphere lobectomy and segmentectomy.

REFERENCES

1. Kappadath SC, Lopez BP, Salem, R, Lam MGEH. Reassessment of the lung dose limits for radioembolization. *Nucl Med Commun*. 2021;42:1064-1075

2. Kao YH, Steinberg JD, Tay YS, et al. Post-radioembolization yttrium-90 PET/CT - part 2: dose-response and tumor predictive dosimetry for resin microspheres. *EJNMMI Research*. 2013;3:57

3. Kao YH, Tan AEH, Lo RHG, et al. Non-target activity detection by post-radioembolization yttrium-90 PET/CT: image assessment technique and case examples. *Front Oncol*. 2014;4:11

4. Kao YH. Dose-response for yttrium-90 resin microsphere radioembolisation. *Nucl Med Commun*. 2021;42:345-347

5. Kao YH, Corlett A, Jorna K, Rhodes A, Sivaratnam D. 90Y PET for qualitative and quantitative assessment of residual activity in delivery apparatus after radioembolization. *J Nucl Med Technol*. 2021;49:178-179

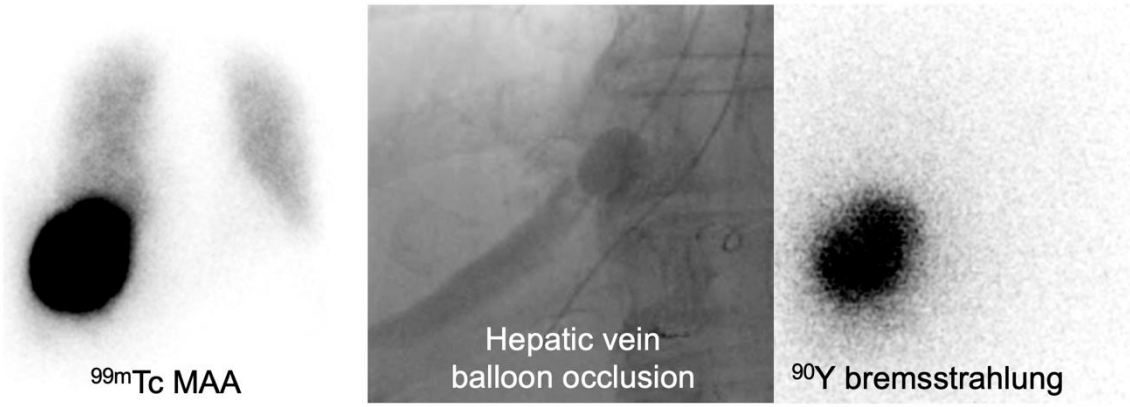
6. Kao YH, Tan AEH, Burgmans MC, et al. Image-guided personalized predictive dosimetry by artery-specific SPECT/CT partition modeling for safe and effective 90Y radioembolization. *J Nucl Med*. 2012;53:559-566

7. Kao YH, Magsombol BM, Toh Y, et al. Personalized predictive lung dosimetry by technetium-99m macroaggregated albumin SPECT/CT for yttrium-90 radioembolization. *EJNMMI Research.* 2014;4:33

8. Schiro BJ, Amour ES, Harnain C, Gandhi RT. Management of high hepatopulmonary shunts in the setting of Y90 radioembolization. *Tech Vasc Interv Radiol*. 2019:58-62

9. Kao YH. Yes, the Holy Gray exists. Learn from modern radioembolisation. *Eur J Nucl Med Mol Imaging*. 2021;48:4115-4117

GRAPHICAL ABSTRACT



Hepatic vein balloon occlusion during radioembolization significantly reduces hepatopulmonary shunting

Figure 1

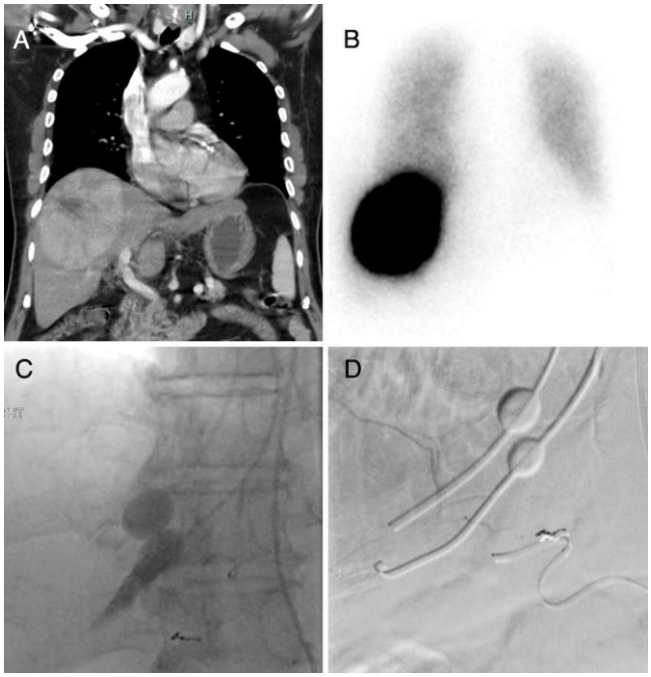


Figure 2