Editorial

# Another hammer, but we need a wrench, and a screwdriver—positron emission tomography/magnetic resonance imaging represents another tool for post-delivery 90Y dosimetry, but what are we still missing?

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*Comment on:* Gurajala R, Partovi S, DiFilippo FP, *et al.* Prospective comparison of positron emission tomography (PET)/magnetic resonance and PET/computed tomography dosimetry in hepatic malignant neoplastic disease after 90Y radioembolization treatment. J Gastrointest Oncol 2024;15:356-67.

**Keywords:** Dosimetry; transarterial radioembolization; positron emission tomography/magnetic resonance imaging (PET/MRI)

Submitted Jun 19, 2024. Accepted for publication Aug 01, 2024. Published online Aug 19, 2024.
doi: 10.21037/jgo-24-460
**View this article at:** https://dx.doi.org/10.21037/jgo-24-460

Selective internal radiation treatment (SIRT) with 90Y radioembolization is increasingly used for the treatment of primary and metastatic liver cancer due to its treatment response and well-tolerated side effect profile (1,2). The primary mechanism of action of SIRT is related to β radiation emission from ~$10^7$ 90Y microspheres, which are selectively delivered to tumors via their feeding arteries (3). β radiation from 90Y travels an average of 2 mm in soft tissues, and the large number of microspheres delivered to a tumor create "clouds" of tumoricidal radiation (4). It has long been observed that the intratumoral distribution of particles delivered via the hepatic arteries is nonuniform (5). To achieve optimal tumor absorbed dose (AD), physicians must consider the total dose delivered to the tumor, as well as mean dose per particle and particle coverage/distribution (6). As will be discussed, the nonuniform distribution of particles creates a challenge for 90Y SIRT both at the time of preimplantation planning dosimetry as well as during post-implantation calculation of AD.

## Nonuniform distribution

Given the dynamic tumor environment, challenges to uniform particle distribution have been recognized and defined as "variations in vascular compartments which affect the geographic deposition of microspheres, resulting in nonuniform patterns of irradiation" (7). Several models aimed to understand this nonuniform distribution point to nonlaminar flow in supplying arteries as a contributing factor (8). Consistent with this are observations that small differences in catheter position, particularly when close to arterial bifurcations, can result in significant differences in distribution (9). However, it is the intratumoral vascular bed that presents a particular challenge to uniform particle distribution due to regions of irregular necrosis, increased interstitial pressure, shunt formation, and capillary attenuation second to any prior systemic therapy (7). For SIRT, these limitations can result in intralesional radiation variability that can compromise dose thresholds for a given portion of the tumor and reduce efficacy (7).

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Nonuniform distribution of embolic particles on the microscopic tumor scale has been demonstrated in a variety of settings, such as in the preclinical VX2 rabbit model using Iron-Oxide containing Embosphere (Merit, South Jordan, UT, USA) particles (10). When analyzed at the microscopic tumor scale, particles are seen to preferentially "clump" within intratumoral end-arteries or nonuniformly arrayed around the periphery of tumor, leading to a relative paucity of particles in some regions.

There are a variety of potential solutions for overcoming or mitigating the challenge of nonuniform particle distribution. Several authors have examined the effects of decreasing the ratio of dose per particle while holding fixed the total dose delivered, as means to improve the uniformity of AD (11). However, this approach may not result in the best clinical outcomes as one group has found per sphere specific activity to be most predictive of achieving complete pathologic necrosis (12). Other groups have assessed the ability of anti-reflux catheters to overcome challenges of increased interstitial pressure and capillary bed resistance (13). However, the issue remains a challenge.

## Overview of 90Y dosimetry

SIRT dosimetry calculations are made in the planning phase (pre-implantation) and after deliver of 90Y microspheres (post-implantation). Pre-implantation dosimetry involves a mapping angiography to identify the hepatic arteries that supply the targeted tumor—ideally including 3D cone beam angiography—and injection of 99m technetium-labeled macroaggregated albumin (99mTc-MAA) for assessment of tumor and normal liver parenchyma within a treatment volume as well as calculation of lung shunt and assessment of any extrahepatic uptake. The distribution of 99mTc-MAA is assessed with single-photon emission computed tomography (SPECT)/computed tomography (CT), such that the 3D gamma uptake is registered to CT data.

Post-implantation, either Bremsstrahlung imaging with SPECT/CT (14) or 90Y positron detection by positron emission tomography (PET)/CT is utilized to perform dosimetry. Given restricted access to PET/CT, which is considered the gold standard (15), either SPECT/CT or simple planar imaging are most utilized. Of note, planar imaging is insufficient to perform advanced or personalized dosimetry. Dosimetry software allows for post-implantation evaluation of actual dose delivered, both to the tumor and normal tissue, and determination of adequacy of lesion coverage (7). Recent advances in dosimetry software facilitate post-implantation voxel-based dosimetry, which allows for the creation of dose volume histograms. Voxel-based dosimetry has been shown to predict tumor response in patients with hepatocellular carcinoma (HCC) (16) and liver metastases (17).

Post-treatment dosimetry is essential to assess the success of a delivery and predict the need for retreatment. It is valuable as a decision-making tool to determine cumulative dose to different compartments with the goal of optimizing tumor response and minimizing toxicity to normal liver. From the perspective of the SIRT as an approach to liver malignancies, accurate post-treatment dosimetry is necessary to determine target dose thresholds and toxicities for tumors of different types and sizes.

While PET/CT is the gold standard for post-implantation dosimetry, PET/magnetic resonance imaging (MRI) is increasingly available in academic centers and provides the metabolic assessment provided by PET with improved tissue contrast, allowing improved demarcation of the tumor on imaging.

## Overview of present article

In this issue of the *Journal of Gastrointestinal Oncology*, Gurajala *et al.* present the first prospective study to assess the inter-modality agreement between PET/MRI and PET/CT 90Y dosimetry (18). At a single institution, 18 patients (20 treated liver tumors) underwent 90Y radioembolization, and post-treatment dosimetry was performed using both PET/CT and PET/MRI, with inter-modality agreement assessed by the Bland-Altman test. Overall, the authors found that inter-modality agreement between PET/CT and PET/MRI was high. While PET/MRI performed well as a method for post treatment dosimetry, it was noted that PET/MRI consistently underestimated tumor and liver ADs when compared to PET/CT by –3.7% (P=0.042) and –5.8% (P=0.029), respectively. Underestimation of AD by PET/MRI has been observed previously (2), and in the present study the authors appropriately infer that the observed inter-modality differences can be attributed to technical limitations in attenuation correction with PET/MRI.

As noted above, post-treatment PET/CT is capable of voxel-based volumetric dosimetry via several Food and Drug Administration approved algorithms, and PET/MRI has been shown capable of this as well (19). The present authors further validate that PET/MRI post-treatment, voxel-based dosimetry can enable assessment of the actual dose distribution in an individual patient. However, two

 

important shortcomings of PET-based post-treatment dosimetry are noted: (I) differences in distribution between pre-treatment 99mTc-MAA evaluated and 90Y therapy drives consistent errors in dose and tumor coverage, and (II) post-treatment PET is limited in its ability to assess particle distribution on the microscopic tumor scale, which prevents accurate analysis of AD.

## Problem 1: pre-implantation distribution

Significant challenges to current pre-implantation SIRT dosimetry relates to inherent limitations of 99mTc-MAA as a scout particle for 90Y. Some studies have shown reasonable agreement between 99mTc-MAA SPECT/CT and post-90Y PET/CT, and DOSISPHERE-01 demonstrated that 99mTc-MAA SPECT/CT can be used with treatment planning software at the time of pre-implantation dosimetry to make clinically beneficial predictions about tumor and liver ADs (20). Largely for the practical reason of its wide availability and the fact that it is bioresorbable, 99mTc-MAA SPECT/CT has remained the standard approach for pre-treatment dosimetry. However, it well established that 99mTc-MAA is not an optimal surrogate for 90Y AD (21,22). Differences in size, morphology, and density between 99mTc-MAA and 90Y contribute to this problem (15).

One theoretical option would be to design a scout particle that is the same size and density as the respective glass or resin therapy, which would be attached to a radiotracer that can be imaged by SPECT/CT (15). Please recall that the short half-life of 99mTc-MAA of 8 hours precludes manufacturing of standardized particles of this type. In spite of much interest, development of such an idealized scout particle has been thus far unsuccessful (15). However, Kokabi *et al.* did demonstrate that using a small dose of 90Y may provide a viable option for this issue (23).

Another option for improved assessment of particle distribution during pre- and post-implantation SIRT dosimetry is to change therapy isotope away from 90Y. The isotope 166Holmium (166Ho) emits high-energy beta radiation which can be used for a therapeutic effect and gamma radiation which can be used for nuclear imaging purposes. 166Ho SIRT has shown efficacy in preclinical experiments and early human studies. A major advantage of 166Ho is that the same isotope is used for pre-implantation and post-implantation imaging, namely therapeutic 166Ho-microspheres (QuiremSpheres™ Holmium-166 Microspheres) and scout 166Ho-microspheres (QuiremScout™ Holmium-166 Microspheres). In fact, studies with 166Ho are some of the most convincing that 99mTc-MAA may poorly predict therapy particle distribution. Smits *et al.* 2020 show representative cases in which there are marked differences between the distribution of 99mTc-MAA and the 166Ho scout dose (24). 166Ho SIRT will be assessed clinically in a forthcoming prospective, single-arm, open-label, multicenter trial in patients with unresectable, early-stage HCC (HOMIE-166). The primary limitation of 166Ho is that pre- and post-implantation dosimetry still rely on SPECT/CT voxel-based dosimetry, which does not achieve resolution at the level of the microscopic tumor distribution.

## Problem 2: post-implantation distribution

In this issue, Gurajala *et al.* show two clinical examples in which time-of-flight PET and PET MRI can detect nonuniform particle biodistribution within targeted tumors post-implantation (18). Having said that, the spatial resolution of PET remains limited due to the low positron count and respiratory motion, which can limit the precision of voxel-based volumetric calculations with PET (25). Further, even idealized voxel-based dosimetry remains a far cry from the precision of understanding particle distribution on the scale of the tumor microenvironment.

The inability to visualize the spatial distribution of particles after delivery limits the accurate assessment of AD within the tumor and surrounding liver parenchyma. Further, accurate assessment of tumor AD establishes the treatment plan for a given tumor or tumors—i.e., just how many total treatment sessions over what timeframe to achieve an expected complete response. Discovering that a significant region of tumor did not receive adequate dose after the fact during post-implantation analysis of AD may result in a delay prior to definitive retreatment. When tumors are inadequately treated in a single session, it raises the possibility of rapid local tumor progression or tumor biology transformation. Improvements in 90Y dosimetry that increase the accuracy of absorbed tumor dose will provide advantages when designing and testing hypotheses around questions of synergistic therapy, namely immunotherapy.

A potential solution is provided by Eye90 (ABK Biomedical Inc., Halifax, NS, Canada), the radiopaque glass 90Y microsphere. The ability to visualize Eye90 on CT and cone-beam CT (CBCT) provides the opportunity to confirm tumor targeting and precisely visualize microsphere

 

deposition post-implantation. This is the first product that facilitates noninvasive assessment of 90Y distribution on the scale of the tumor microenvironment. Accordingly, it has the potential to quantify accurate post-implantation dose to target tumor.

## Conclusions

The future of SIRT is bright but will require a concerted effort to improve our dosimetry tools, particularly as we look to designing trials that combine precise treatment timing in synergy with one or more additional therapies, such as immune checkpoint inhibitors and/or coincident activation of the innate arm of the immune system utilization of intramural injection, alteration of the tumor microenvironment via free radical formation or hypoxia. Optimal treatment of liver tumors will not simply remain as a dumping of a massive dose into a small treatment angiosome, particularly as we consider treatment of liver tumors other than HCC, such as infiltrative tumors, e.g., cholangiocarcinoma, where the precise margins between tumor and liver parenchyma are blurred, or poorly vascular tumors, e.g., colorectal cancer, within which the effects of nonuniform particle distribution will likely be exacerbated. In order for SIRT to prove benefit for these challenging tumor types, tumor dosimetry will matter. Nailing down precise particle distribution during pre- and post-implantation analysis will be essential to the dosimetry toolkit.

## Acknowledgments

*Funding:* None.

## Footnote

*Provenance and Peer Review:* This article was commissioned by the editorial office, *Journal of Gastrointestinal Oncology*. The article did not undergo external peer review.

*Conflicts of Interest:* Both authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-460/coif). S.Y. reports that he has received consulting fees, been a part of the speaker bureau, and received funds for travel from Boston Scientific. He has also received consulting fees from Mirada and Teledaas Varian as well as served in leadership roles for both the Society of Interventional Radiology and the GEST meeting. G.W. reports that he received funds for travel from Boston Scientific. The authors have no other conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.



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**Cite this article as:** Woodhead G, Young S. Another hammer, but we need a wrench, and a screwdriver—positron emission tomography/magnetic resonance imaging represents another tool for post-delivery 90Y dosimetry, but what are we still missing? J Gastrointest Oncol 2024;15(4):2006-2010. doi: 10.21037/jgo-24-460

 