Standard Radiation Dosimetry Models: What Interventional Radiologists Need to Know

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Abstract

Thoughtful and accurate dosimetry is critical to obtain the safest and most efficacious yttrium-90 (Y90) radioembolization of primary and secondary liver cancers. Three dosimetry models are currently used in clinical practice, namely, body surface area model, medical internal radiation dose model, and the partition model. The objective of this review is to briefly outline the history behind Y90 dosimetry and the difference between the aforementioned models. When applying these three models to a single case, the differences between them are further demonstrated. Each dosimetry model in clinical practice has its own benefits and limitations. Therefore, it is incumbent upon practicing interventional radiologists to be aware of these differences to optimize treatment outcomes for their patients.

Keywords
- Y90
- Dosimetry
- Partition Model
- BSA model
- MIRD model
- Yttrium-90
- Radioembolization

Yttrium-90 radioembolization (Y90-RE) is a form of internal radiotherapy utilized for the treatment of both primary and secondary hepatic malignancies.[1–9] Radioembolization, the preferred treatment nomenclature,[10] is also referred to synonymously as selective internal radiation therapy. Yttrium-90 microspheres are delivered directly into the hepatic arteries which are the predominant supply of the hepatic tumors.[11] The mechanism of action for Y90-RE tumor treatment is radiation-induced necrosis from the transarterial administration of Y90 microspheres.[12] Y90 predominantly emits β-radiation, has a 64.2-hour half-life, and delivers most of its radiation (94%) within the first 11 days.[12] Two types of yttrium-90 microspheres are commercially available in the United States—glass microspheres, TheraSphere (Boston Scientific, Marlborough, MA)[13] and resin microspheres, SIR-Spheres (Sirtex Medical Limited, Woburn, MA).[11,14] The average size of resin microspheres is larger than its glass counterpart, with a median diameter of 32.5 microns (range: 20–60 microns). Glass microspheres have a diameter range of 20 to 30 microns.[15,16] The mean specific activity per sphere varies between products; glass microspheres have an activity as high as 2,500 Bq per sphere, while resin microspheres have an activity of 150 Bq per sphere in 3-day precalibrated format. Necessarily, the inherent differences affect the number of microspheres administered to achieve a prescribed activity.[15,17,18] Multiple guidelines, such as those of National Comprehensive Cancer Network (NCCN)[19] and the American Association for the Study of Liver Disease,[20] consider the use of Y90-RE as a treatment option for hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma, and hepatic metastases.[21,22] Nevertheless, multiple randomized phase 3 trials such as the SIRveNIB and SARAH showed no improvement in overall survival (OS) in HCC with selective internal radiotherapy when compared with the chemotherapeutic, sorafenib.[23–25] However, the failure to demonstrate superiority does not necessarily mean Y90 is equivalent to sorafenib.[26] Specifically, a common criticism of many "failed" Y90 trials including SARAH and SIRveNIB is the absence of personalized dosimetry included in the trials. Moreover, post hoc dosimetry analysis of the SARAH trial demonstrated that patients with HCC who received intratumoral Y90 dose of at least 100 Gy had a significantly prolonged median OS of 14.1 versus 6.1 months for others.[27] Additionally, the phase 2

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DOSISPHERE-01 trial demonstrated that delivery of personalized dosimetry significantly improved objective response rates and prolonged OS in patients with locally advanced HCC, suggesting that personalized dosimetry is critical to improve outcomes in clinical practice.[28] The goal of this review is to provide a brief history of dosimetry, an overview of the relevant models in practice, and a case example to illustrate clinical implications of different dosimetry models for practicing interventional radiologists and trainees.

A Brief History of Dosimetry

The first reported use of radioembolization with Y90 microspheres was to treat colorectal cancer that had metastasized to the liver in animals and two human subjects.[12,29] Subsequent expansion of the technology used Y90 to treat HCC.[30–32] The first attempt to perform dosimetry from Y90 delivery to the liver was in 1965, where a 10-patient clinical trial revealed the exact dosage was difficult to calculate without knowledge of the distribution of isotopes after administration. The investigators assumed a uniform distribution, ignoring the differences between distribution within tumor and nontumoral liver while admitting that to be a shortcoming of their estimations.[33] In the next 20 years, the body surface area (BSA) model was created, which calculated activity to be administered in the form of resin microspheres based on BSA and later on tumor extent.[34] During this time, treatment-related toxicities such as myelosuppression, pulmonary fibrosis, and gastritis were seen and believed to be related to the inability to accurately calculate radiation dosages to different compartments. To build upon creating a more accurate Y90 dosimetry model, a 15-patient trial used technetium-99 (Tc-99)-labeled macroaggregated albumin (MAA) to determine liver–lung shunt fraction (LSF) prior to glass microsphere treatment, CT imaging to estimate liver volume, and a posttreatment bremsstrahlung scan to confirm hepatic Y90 delivery and exclude inadvertent extrahepatic activity. This study created what is now known as the medical internal radiation dose (MIRD) model.[35]

Because HCC is currently the most well-studied pathology for Y90-RE dosimetry, we will focus on HCC in this review. The pathophysiology for treating HCC and other primary and metastatic liver tumors with radioembolization lies in the tumors' unique blood supply. HCC preferentially induces angiogenesis from the hepatic arterial supply instead of the portal venous system.[36] In a similar way, metastatic tumors also derive the majority of their blood supply (80–100% for tumors > 3 mm) from the hepatic arterial system.[37] The tumoricidal effect of radioembolization is primarily mediated by radiation injury, and specifically through induction of indirect cellular DNA damage through free radical generation.[38,39]

The goal of radioembolization therapy depends on overall tumor burden and goals of care. Patients can be categorized into two treatment groups: curative intent and palliative intent. For those undergoing treatment with curative intent, there are two treatment options—radiation segmentectomy (Y90-RS) or radiation lobectomy (Y90-RL). In patients undergoing treatment with palliative intent, treatment is personalized to delay disease progression and maintain quality of life regardless of the tumor presentation as unilobar, bilobar, or with macrovascular invasion.[40] To achieve these goals of care, it is necessary to understand how the dosage of radiation is calculated when performing a radioembolization to achieve the safest and most efficacious possible patient outcomes.[28,41] Currently, there are three Y90 radioembolization dosimetry models used in clinical practice: the BSA model, MIRD model, and the partition model. As a treating interventional radiologist, it is critical to understand and interpret all these models to maximize treatment goals and minimize treatment-related complications.

Standard Models in Practice

Body Surface Area Model

Commonly used for resin microspheres as the recommended model in SIR-Sphere package insert,[42] the body surface model calculates the prescribed activity for each patient using only the BSA formula and the tumor burden within the targeted tissue.[12,43]

$$A[\mathrm{GB_q}] = (\mathrm{BSA} - 0.2) + \frac{v_t}{v_t + v_n}$$

A[GBq] is the activity within the target tissue, v_t is the tumor volume, and v_n is the normal tissue volume. BSA is calculated using the Du Bois BSA formula[44]:

$$\mathrm{BSA}\ (\mathrm{m}^2) = \text{weight in kg}^{0.425} \times \text{height in centimeters}^{0.725} \times 0.007184.$$

The BSA model is simple and easy to calculate. Despite the ease of dose calculation, two treatment contraindications to consider when using this model are greater than 20% lung shunting or greater than 30 Gy radiation dose absorbed to the lungs (as estimated by Tc-99-MAA scan).[15] In addition, the BSA model has limited personalization and does not allow adjustment to calculate absorbed radiation dose of the tumor tissue versus surrounding nontumoral liver tissue. For large tumors/area to be treated, the BSA model can undertreat because it artificially limits Y90 activity between 1.0 and 3.0 GBq.[43] Additionally, there is low correlation between BSA and liver volumes, which can result in significantly lower activity concentrations in patients with larger livers.[45] On the other hand, there is the potential to overdose obese patients with a relatively normal liver volume with respect to the patient's size (►**Table 1**).

Medical Internal Radiation Dose Model

Recommended by the manufacturer of glass microspheres, the MIRD model was updated in 1975.[46] The current, clinically used MIRD model calculates administered activity using the following formula:

$$A_0[\mathrm{GB_q}] = \frac{D[\mathrm{Gy}] \times \text{ mass of liver [kg]}}{50 \times (1 - \frac{\mathrm{LSF}}{100})}$$

Table 1 Dosimetry models, equations, and limitations

	Equation	Benefits	Limitations
BSA	$A_0[\mathrm{GB_Q}] = (\mathrm{BSA} - 0.2) + \frac{v_t}{v_t + v_n}$	- Simple - Easy to calculate - Can consider dose reductions based on LSF - Model recommended by SIRTex resin microspheres	- Limited personalization - No consideration of tumor dose based on ratio of tumor to normal liver tissue - Y90 activity limited to 1.0–3.0 GBq - Tumor radiation dose is unknown - Possibility to undertreat
MIRD	$A_0[\mathrm{GB_q}] = \frac{D[\mathrm{Gy}] \times \text{mass of liver [kg]}}{50 \times (1 - \frac{\mathrm{LSF}}{100})}$	- Simple, single model - Consistent and reproducible estimates	- Does not differentiate the dose given to tumor vs. normal liver parenchyma - Y90 microsphere administration is not uniform in practice - Possibility to overtreat
Partition	$A_0[\mathrm{GB_q}] = \frac{(D[\mathrm{Gy}] \times \frac{T}{N} \times \text{tumor mass [kg]})}{(50 \times (1 - \mathrm{LSF}))}$	- Accounts for different compartments - Allows calculation of tumor, nontumor, and lung dosages	- More complex to calculate - Relies on Tc-99-MAA as surrogate for Y90 microsphere biodistribution - Assumes uniform distribution in each compartment

Abbreviations: BSA, body surface area; LSF, lung shunt fraction; MAA, macroaggregated albumin; MIRD, medical internal radiation dose.

A_0[GBq] represents the activity to be administered, D[Gy] is the dose delivered into the liver lobe/segment in Gray, and 50 is a rounded constant derived from the Y90 isotope characteristics.[40] Further information on the derivation of the MIRD formula is covered elsewhere.[40,47,48]

The MIRD model is a single-compartment model that assumes uniform activity distribution within the target tissue. However, the targeted tissue contains tumor and nontumor liver parenchyma; this is precisely the major limitation of this model. In settings of severe cirrhosis or emphysema, this model can underestimate dose to the liver or lung because the model presumes radiation absorption will be the same as normal liver or lung tissue,[48] potentially leading to overtreatment of patients.[49] Benefits of the MIRD model include its ease of calculation and its consistent and reproducible dose estimates.[47]

Partition Model

Dependent on Tc-99m-MAA single-photon emission computed tomography (SPECT)/CT modeling, the partition model is more complex, incorporating tumor, nontumor liver, and lung components. This model is hypothesized to minimize radiation-induced hepatotoxicity compared with BSA and MIRD models.[50]

$$A_0[\mathrm{GB_q}] =/ \frac{(D[\mathrm{Gy}] \times \frac{T}{N} \times \text{tumor mass[kg]})}{(50 \times (1 - \mathrm{LSF}))}$$

A_0[GBq] represents the activity in the targeted liver tissue, D[Gy] is the desired tumor dose in Gray, T/N is the relative uptake of tumor versus normal liver, and LSF is the lung shunt fraction. This model is technically more complex and incorporates multiple compartments (liver, tumor, and lung), making it more accurate to use. This model allows for activity administration in which tumor, nontumor liver, or lung doses can be separately calculated and used as the thresholds. However, the Partition model is limited by the use of Tc-99-MAA due to inconsistencies in biodistribution compared with Y90 microspheres and also from variability in catheter position upon dose administration.[51] Additionally, the model assumes uniform distribution of the activity in each compartment,[52] which is not an accurate assumption.

Case Example: Dosimetry in Practice

Recommended General Planning and Treatment Algorithm

At our institution, patients first undergo vascular mapping and Tc-99m-MAA shunt studies using planar and SPECT/CT to determine LSF, extrahepatic activity, and T/N if the partition model is being used. Additionally, cone beam CT (CBCT) is utilized during the mapping study to ensure complete tumor perfusion is through the subselected vessel(s). Coiling/plugging is performed as needed to minimize the risk of nontarget embolization. It is critical to ensure complete tumor perfusion is identified on mapping to enable proper treatment planning. Preferably, the circumstances of Tc-99m-

MAA administration are replicated for the planned therapy including use of the same microcatheter and delivery from the same vascular location. After the desired administered activity is calculated based on the treatment intent and the dosimetry model used, the patient is brought back to interventional radiology for the therapy session. From the same microcatheter position (or positions of split activity administration) that the MAA was administered and again after confirming complete perfusion of the tumor both on mapping CBCT and MAA SPECT/CT, prescribed Y90 activity will be administered. Patient will then undergo Y90 bremsstrahlung SPECT/CT again to ensure complete targeting of the tumor and absence of nontarget embolization. Post-Y90 administration dosimetry can also be performed to ensure delivery of treatment goal doses to the tumor and nontumoral liver parenchyma.

Patient Case

A 65-year-old man with a past medical history of hepatitis C–induced cirrhosis presented with a 2.9-cm HCC tumor in segment 6 of his liver. Based on laboratory, imaging, and clinical assessment, he was an orthotopic liver transplant candidate classified as Child–Pugh A, Eastern Cooperative Oncology Group score 0 (ECOG-0), and Barcelona Clinic Liver Cancer stage A (BCLC-A). He was referred to the interventional radiology clinic for bridging therapy and Y90 was thought to be the most appropriate treatment for this patient. Baseline MRI demonstrated an avidly enhancing lesion with washout in segment 6 (►**Fig. 1a**). On mapping angiography (►**Fig. 1b**), the patient was noted to have a hypervascular tumor supplied by two small branches of the right hepatic artery, one arising from the anterior right hepatic artery and one from the posterior. These branches were not amenable to selective catheterization due to size and risk of vasospasm. The decision was made to plan the treatment to the entire right lobe. CBCT was then performed (►**Fig. 1c**) prior to MAA administration (►**Fig. 2a**) to ensure complete coverage of the tumor and absence of potential nontarget embolization. Tc-99-MAA was administered from the microcatheter location where CBCT was performed. The Tc-99-MAA SPECT study confirmed complete coverage of the targeted tumor with no extrahepatic activity (►**Fig. 2b**). The LSF was calculated to be 4.6% with a Tumor to Normal Ratio (TNR) of 3.9.

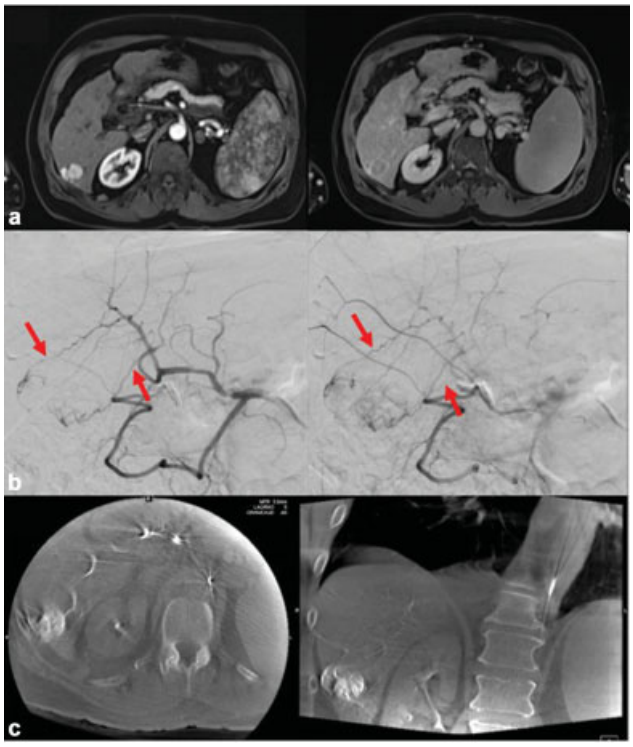

Fig. 1 (**a**) Pretreatment, avidly enhancing hepatocellular carcinoma tumor seen in segment 6. (**b**) The red arrows denote the feeding arteries visualized by selective right hepatic angiography. (**c**) Cone beam CT (CBCT)—use of CBCT ensures complete coverage of the tumor from the location of the microcatheter where macroaggregated albumin is to be administered.

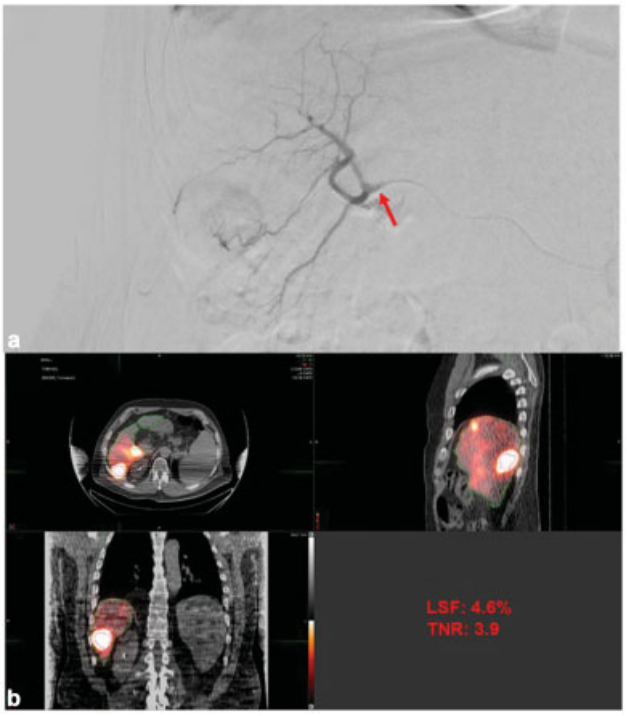

Fig. 2 (**a**) Tc-99-macroaggregated albumin (MAA) injection and (**b**) Tc-99-MAA single-photon emission computed tomography confirm complete coverage of the targeted tumor with no extrahepatic activity.

Treatment was planned using MIRD model with delivery of 80 Gy to the right lobe using SIR-Sphere. The treatment plan was based on the SARAH trial data, which demonstrated that tumor dosage of 100 Gy or more improves tumor response and prolongs survival.[53] Given the hypervascular nature of the tumor, greater than 100 Gy was projected to be delivered to the tumor. Accordingly, 2.2 GBq of activity was administered to the right hepatic artery.

Prescribed Y90 activity was then administered from the same microcatheter position from which Tc-99-MAA was administered and using the same type of microcatheter (2.8 Fr Progreat; Terumo Medical Corporation, Tokyo, Japan). The patient then underwent confirmatory Y90 SPECT/CT. Post-administration dosimetry using MIM SurePlan (MIM Software, Cleveland, OH) was performed to ensure adequate dose was delivered to the tumor (►**Fig. 3a**). We contoured the liver

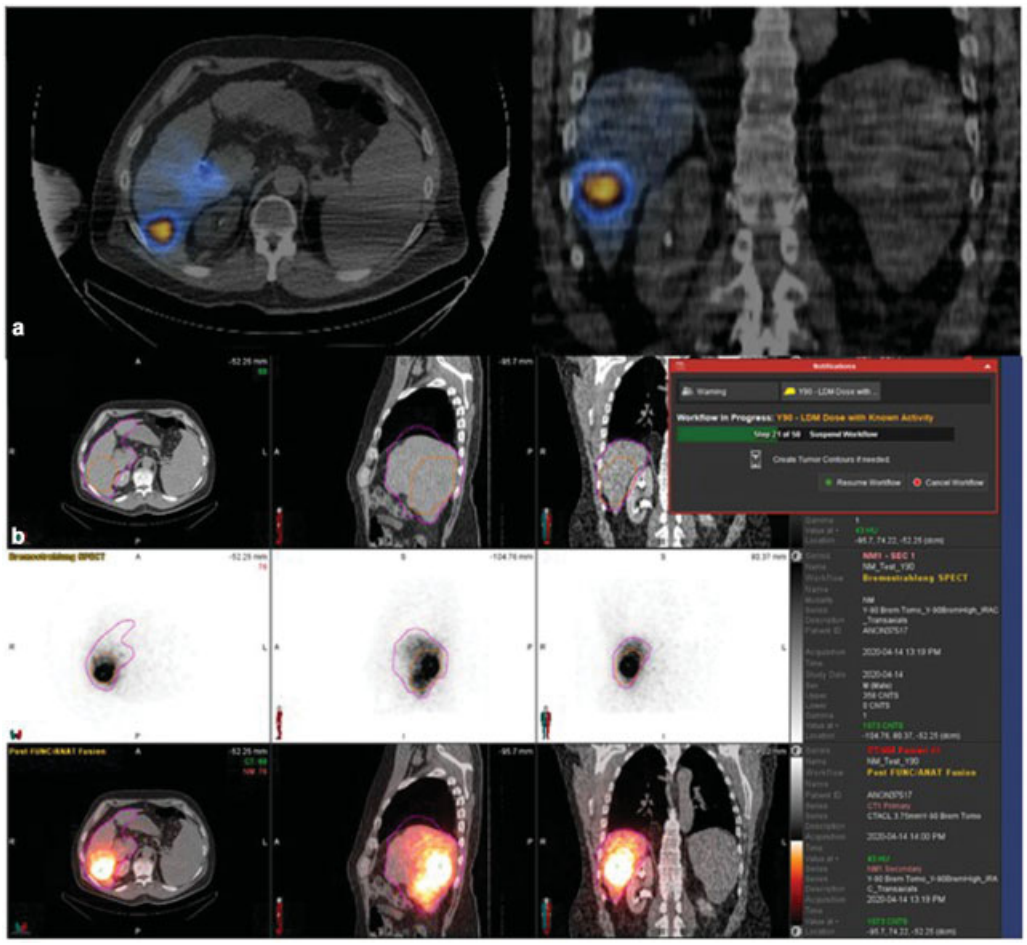

Fig. 3 Actual treatment: (**a**) Bremsstrahlung single-photon emission computed tomography (SPECT) calculation of administered activity (**b**) Posttreatment Y90 SPECT/CT confirming Y90 administration.

and tumor on contrast-enhanced MRI or CT which then was fused to the Y90 bremsstrahlung SPECT/CT (►**Fig. 3b**). The calculated dose delivered to the tumor was 303 Gy, while the dose to the nontumoral liver was 73 Gy, which is above the recommended target dose to nontumoral liver when treating with resin microspheres.[54] Dynamic contrast-enhanced MRI 6 weeks posttherapy demonstrated complete response in the targeted tumor (►**Fig. 4**). At 6-month follow-up, the patient continued to have non-viable treated tumor with no treatment-related toxicity.

►**Table 2** demonstrates the projected differences in dose delivered to each compartment (i.e. tumor, non-tumoral liver and lung), had we used BSA model, MIRD model with the goal of 120 Gy to the perfused liver segment/lobe, and partition model with the goal of 200 Gy to the tumor.

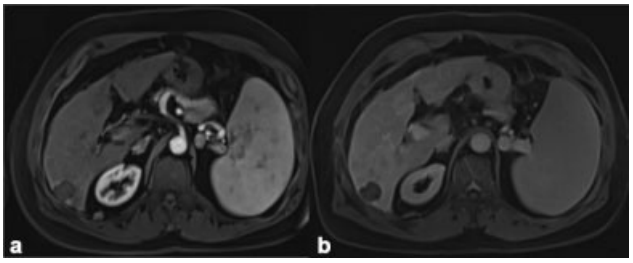

Fig. 4 Six weeks posttherapy, magnetic resonance imaging demonstrates complete response seen on both arterial (**a**) and portal venous (**b**) phases of study with preserved liver function.

Using MIRD model with the goal of 120 Gy to the infused right liver lobe, 424 Gy would be delivered to the tumor which would be considered over treatment for HCC treated with resin microspheres. More importantly, nontumoral liver dose of 109 Gy would significantly increase the risk of hepatotoxicity given the size of the area treated. Had we used the BSA model, which is the recommended model to be used for resin microspheres, 183 Gy would be delivered to the tumor which would be probably tumoricidal based on available evidence[27] and 47 Gy to the nontumoral liver which is considered a safe threshold by many experts. On the other hand, had we used the partition model, we could ensure delivery of 200 Gy to the tumor while delivering 51 Gy to the liver which is probably the upper limits of nontumoral liver dose to minimize significant hepatotoxicity.[54,55] Finally, using the actual treatment planning strategy employed in this case, we probably overtreated the tumor which means delivering higher than desired dose to the nontumoral liver which could cause liver toxicity.

In conclusion, as illustrated in the example earlier, and throughout this article, each Y90 dosimetry model in current

Table 2 Prescribed activity and dose delivered to each compartment using different dosimetry models

Actual administered activity and dose to different compartments					
	Actual administered activity	**Tumor dose**	**Nontumor liver dose**	**Lung dose**	**Notes**
Mean activity (range)	2.2 GBq	303 Gy (925–0 Gy)	73 Gy (326–0 Gy)	5.1 Gy	
Projected dose to different compartments using different dosimetry models					
	Calculated administered activity	**Tumor dose**	**Nontumor liver dose**	**Lung dose**	**Notes**
BSA	1.4 GBq	183 Gy	47 Gy	3.7 Gy	Height: 5′ 10″ Weight: 78 kg
MIRD w/ 120 Gy to the perfused lobe	3.4 GBq	424 Gy	109 Gy	8.5 Gy	Treated liver: 1,350 cc
Partition model	1.8 GBq	200 Gy	51 Gy	4 Gy	

Abbreviations: BSA, body surface area; MIRD, medical internal radiation dose.

clinical practice has pros and cons with significant clinical implications. It is incumbent upon practicing interventional radiologists to know the clinically significant differences between these models to ensure the best treatment outcomes for their patients.

Conflicts of Interest

N.K. receives funding from SIRTEX Medical. R.T.G. discloses a relationship with Sirtex as a proctor, speaker, and consultant. R.G. is a proctor and consultant for Sirtex. All other authors declare no conflict of interest.

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