Down and Dirty With Dosimetry

A practical understanding and approach to radioembolization.

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The majority of hepatic arterial therapies that utilize carrier-based delivery mechanisms (eg, chemoembolization and drug-eluting beads) rely on the embolic phenomena to contribute to radiographic and clinical response.[1,2] Transarterial radioembolization (TARE) operates on a completely different basis due to the fact that the primary mechanism of action is the radiation source, not the physical microsphere. The radioactive microsphere is substantially smaller (20–60 µm) than bland and drug-eluting microspheres (60–700 µm)[3,4] and does not illicit an ischemic or anoxic event. Thus, in the case of TARE, the primary mechanism of action is the cumulative damage through the generation of oxygen free radicals derived from radioactive decay. As a result of this mechanism, TARE is driven by the amount and distribution of radioactivity deposited within the tumor, liver, and extrahepatic anatomy (secondary to shunting), which is a function of the number of particles and amount of radioactivity loaded on each particle. General recommendations with respect to clinical activity determination methods have been established by the Radioembolization Brachytherapy Oncology Consortium (REBOC).[5]

WHAT IS ACTIVITY, AND HOW DOES IT DIFFER FROM DOSE?

Before delving into the activity determination methods, a simple review of the definition of terms is required. The concepts and terminology can sometimes be confusing to the user because although there is a relationship between the activity and dose, it is not completely linear. *Dosimetry* is defined as the amount of absorbed dose delivered by ionizing radiation. *Absorbed dose* is the fundamental quantity defined as the mean energy imparted by the radiation per unit mass. The common SI unit for radioactivity is the becquerel (Bq), which is commonly measured in gigabequerel (GBq) in TARE, but also referenced as millicurie (mCi). The activity (GBq or mCi) when deposited into a specific volume of specific tissue results in a distribution of energy, referred to as *dose* (Gy).

Confusion also exists with respect to the compartmentalization of radiation when discussing TARE. Ultimately,

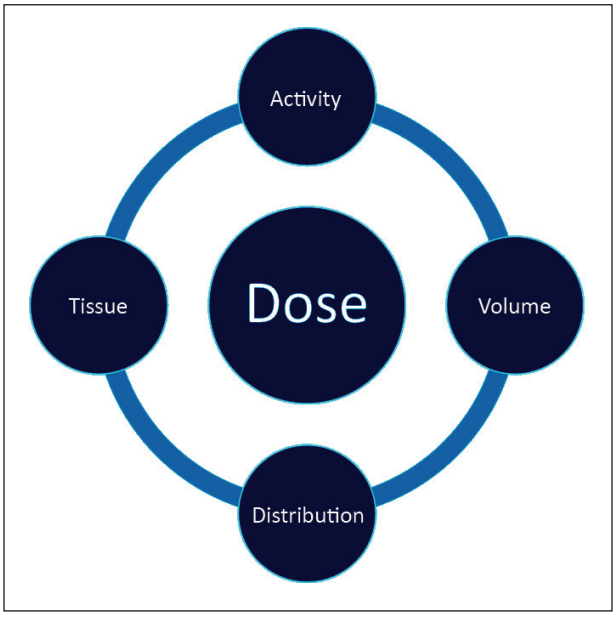


Figure 1. The relationship between dose and activity, volume, distribution, and tissue. Dose (measured in Gy) is dependent on overall activity (mCi or GBq), volume (mL), radiation weighting factor of tissue (WR), and distribution of radiation sources (number of overall particles and the relative homogeneity of the distribution).

TABLE 1. FACTORS THAT AFFECT DOSE/ACTIVITY

Method	BSA	Amount of Liver	Liver Tissue Volume	Tumor Fraction	Overall Volume Dose	Target Dose Tumor	T/N Ratio
BSA	✓	✓		✓			
MIRD			✓		✓		
Partition		✓	✓			✓	✓

Abbreviations: BSA, body surface area; MIRD, medical internal radiation dose; T/N, tumor to normal.

in the setting of TARE, the absorbed dose with any unit of tissue will depend upon (1) the number of particles that distribute within the tissue, (2) the specific activity of the particles within the tissue, and (3) the susceptibility of the tissue to the radiation exposure and the volume of the target (Figure 1). Therefore, the activity administered to a theoretical volume of the entire liver may (and ideally should) distribute in a disproportionate amount to the tumor as opposed to the liver.

Of note, the determination of activity in all current "dosimetry calculators" implemented for TARE does not reflect real-world tumor dose or liver parenchymal dose and represent gross oversimplifications of tumor architecture and radiobiology. With this in mind, a brief description of the currently applied activity models is outlined in the following section.

Clinical Methods of Activity Determination

Currently, there are only two commercially available yttrium-90 (Y-90) radioembolic microsphere platforms approved for clinical use. There are significant differences in design and technical specifications between glass radioactive microspheres (TheraSphere, BTG International) and resin microspheres (SIR-Spheres, Sirtex Medical Inc.) with respect to production, delivery, and logistical implementation that are beyond the scope of this article. However, it is important to note that the primary difference between the two physical particles relates to the estimated specific activity per particle (ie, Bq per sphere), or in other terms, the number of particles per unit of activity. This has significant implications to the statistical distribution of particles (and thus energy) and may also significantly affect the dosimetry of the target tumor, as well as the liver. Current basic methods of activity determination include the body surface area (BSA), medical internal radiation dose (MIRD), and partition models (Table 1).

BSA method. The BSA method is the most common method used for determining resin microsphere activity. Taking into account the theoretical normal liver volume relative to BSA with compensation/increase in activity for increasing tumor burden, the equation as described in the United States instructions for use (IFU) for resin microspheres is shown in Table 2.

As noted in the equation, overall activity in dosimetry loosely correlates with the degree of tumor infiltration within a target volume. The BSA equation does not take into account the actual activity (or its distribution) deposited into the liver and tumor. Despite this

TABLE 2. BASIC METHODS OF ACTIVITY DETERMINATION FORMULAS

Method	Formula	Notes
BSA	Activity (GBq) = (BSA − 0.2) + (% tumor involvement ÷ 100)	BSA is measured in m^2/kg
MIRD	Activity (GBq) = ([desired dose] × [liver mass]) ÷ 50	Desired dose is measured in Gy; liver mass is measured in kg
Partition	$\text{Activity} = \frac{(\text{target dose to tumor} \cdot MT \cdot [VT \cdot T/N + VL] \times 100)}{(49.7 \cdot VT \cdot T/N \cdot [100 - \text{lung shunt}])}$	Lung shunt is measured in %; MT, mass of tumor (kg); VT, volume of tumor (L); VL, volume of normal liver parenchyma (L); T/N, tumor to normal ratio

A

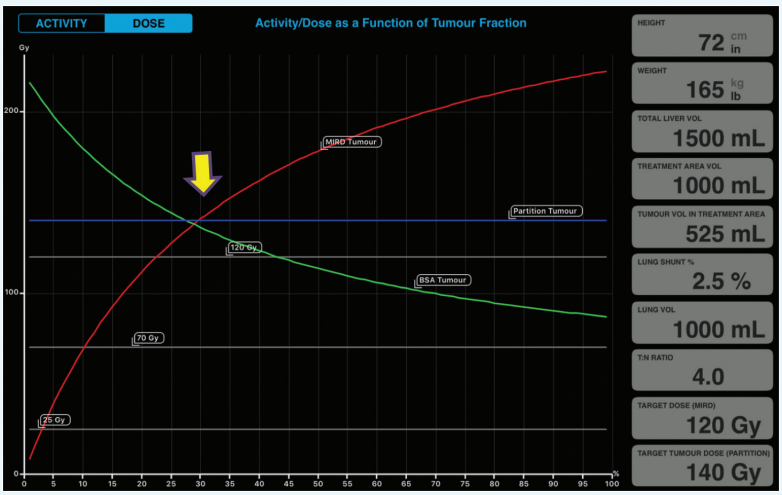
MIRD	DOSE	ACTIVITY
TUMOUR	181.7 Gy	2.0 GBq
LIVER	45.4 Gy	0.4 GBq
LUNG	3.0 Gy	0.1 GBq
TOTAL		2.5 GBq

BSA	DOSE	ACTIVITY
TUMOUR	111.5 Gy	1.2 GBq
LIVER	27.9 Gy	0.3 GBq
LUNG	1.8 Gy	0.0 GBq
TOTAL		1.5 GBq

Partition	DOSE	ACTIVITY
TUMOUR	140.0 Gy	1.5 GBq
LIVER	35.0 Gy	0.3 GBq
LUNG	2.3 Gy	0.0 GBq
TOTAL		1.9 GBq

HEIGHT 72 cm / in
WEIGHT 165 kg / lb
TOTAL LIVER VOL 1500 mL
TREATMENT AREA VOL 1000 mL
TUMOUR VOL IN TREATMENT AREA 525 mL
LUNG SHUNT % 2.5 %
LUNG VOL 1000 mL
T:N RATIO 4.0
TARGET DOSE (MIRD) 120 Gy
TARGET TUMOUR DOSE (PARTITION) 140 Gy

B



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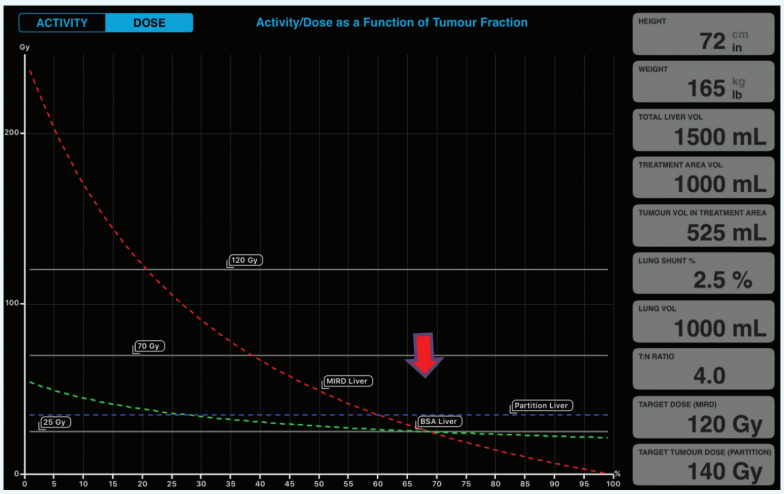

Figure 2. Illustration of the relationship between methods of calculation providing a more global perspective of the relationship of dose and activity of each compartment as a function of the amount of tumor in the target compartment. The relationship arithmetically changes with each of the variables along the right column and thus is different for every patient. Note: Graphs were plotted and created utilizing a dosimetry and activity visualization calculator (DAVYR), a free iPhone and iPad app developed by one of the authors (Dr. Liu), and is available at the Apple App Store or at https://appsto.re/us/vz539.i. With the variables entered along the right column, panel A illustrates the total amount of activity to be injected with each calculation method (BSA, MIRD, and partition) under the row labeled "total." The individual compartments (liver, tumor, and lung) are then determined, along with the estimated dose (not taking into account distribution within each compartment). A wide variation in activity is seen. Panels B and C show the liver dose relationship to tumor volume, in which the y-axis denotes dose to the tumor (solid lines) (B) and tumor (hashed lines) (C) as a function of the percentage of tumor within the target treatment volume, and the x-axis represents the continuous function of the percentage of tumor infiltration in the area targeted in the liver. The overlap of dose relating to tumor compartment occurs when 27% tumor infiltration occurs (yellow arrow). Panel C demonstrates a safety margin of liver parenchyma dose using BSA and partition models through all degrees of tumor infiltration and safety utilizing MIRD when > 40% tumor burden is present (red arrow). Deviations of parenchymal and tumor dose are significant when using MIRD and BSA and become more pronounced as tumor burden/fraction increases (in illustrated case, panel B > 40%).

limitation, the BSA method has been effectively utilized for resin microspheres in several randomized controlled trials.[6,7] This method generally results in the lowest overall amount of calculated activity in most clinical scenarios. Theoretically, the larger number of particles (ie, the lower specific activity) may result in more uniform distribution of radiation (and a more uniform dose) within the liver and the tumor; however, the clinical consequences of this phenomenon are unknown.

MIRD method. The MIRD methodology is utilized primarily for glass microsphere administration. The equation, as described in the United States IFU for glass microspheres with a recommended dose to the liver between 80 to 150 Gy is shown in Table 2. The liver volume (and corresponding liver mass) may be determined using CT, MRI, or ultrasound scans.

The compartmentalization and preferential uptake of particles into the hepatic arterial supply are not taken into account utilizing this methodology.[8] As such, this method of activity determination may result in high variations of dose reaching the liver parenchyma (eg, cases of low tumor burden or hypovascular lesions) and potentially even higher activity within the tumor itself (eg, small- to medium-sized hypervascular lesions). Nonetheless, safety data relating to hepatocellular carcinoma and colorectal carcinoma have suggested that acceptable toxicities are achieved when this method is applied to glass microsphere administration.[9-11]

Partition model. The partition model, originally developed in the early 1990s, represented the first (and theoretically the most accurate) method of estimating theoretical activity/dose partitioned into the liver, lung, and tumor compartment.[12-14] By incorporating the relevant variables of tumor volume, liver volume, shunt fraction, tumor to normal (T/N) ratio uptake, and vascular anatomy, compartmental dose and activity can be determined based on the formula shown in Table 2.

A fundamental false assumption is that all compartments receive their respective activity in a uniform and homogenous manner and have uniform dose throughout their distributions. Limitations include the potential for labor-intensive determination of liver and tumor volumes (although software is available to assist in these calculations), difficulty in measuring volumes in biliary disease presentation, and the potential inability to determine the true T/N ratio.

WE DON'T KNOW WHAT WE DON'T KNOW

The oversimplification of the concepts surrounding dose have resulted in both confusion and ambiguity, not only when comparing the two commercially available products, but also with respect to what constitutes a safe dose to the liver and an effective target dose to the tumor. In the case of TARE, dose is key to understanding both tumor response as well as mitigation of complications arising from excessive radiation exposure to the liver parenchyma. The objective is not to maximize radiation, but rather to optimize it in a fashion such that the dose to the tumor is tumoricidal, while minimizing exposure to otherwise functional liver parenchyma.

Lewandowski et al demonstrated the feasibility of delivering prolonged-decay glass microspheres, resulting in a larger number of particles delivered per unit of radioactivity up to 14 days from calibration.[15] With a 64.2-hour half-life, extension to 14 days after calibration leads to a 40-fold increase in the number of particles, within the range of particles utilized in resin microsphere administration.[4] In the earlier literature, an increased incidence of stasis was reported with resin microspheres utilizing BSA models. Since these initial reports, both animal study and clinical outcomes have demonstrated that the stasis phenomenon was primarily due to the use of sterile water as a suspension agent during administration (which is vasospasmotic and a sclerosant), and the issue has largely been addressed with a conversion to the use of 5% dextrose in water as the infusate.[16]

In the literature that evaluates glass microspheres, when the partition model is retrospectively applied to patients with hepatocellular carcinoma who responded to therapy (200–500 Gy),[17,18] the wide variation in the number of particles (ie, the distribution of particles) relative to a given activity may account for the wide range of optimal tumor target dose. Thus, tumoral coverage may factor into the response. This may also explain the relatively stable target tumor dose range of 100 to 120 Gy, as described in the resin microsphere literature, which is generally not modulated in the clinical setting.[14,19]

As such, the discussion of dose in its current manifestation is restricted to a mathematical compartmentalization of radiation exposure and assumes uniform exposure of a fixed compartment with a fixed amount of radiation, which by the nature of tumoral and hepatic architecture, is fundamentally incorrect.[20]

Thus, as per the commentary provided by Spreafico et al, a deeper understanding of the modulation and efficacy of response should include a function related to the number of particles and the specific radioactivity distributed in these particles. This would allow a better context to discuss the nuance of dosimetry within an

individual compartment as a reflection of particulate (and activity) distribution.[21] The so-called EX protocol with glass microspheres has established a larger number of particles (termed "embolic load") to be a safe and potentially effective method in increasing the number of glass microspheres per administered activity in order to improve distribution of radioactivity. Controversy regarding how to optimize the method of delivery and activity calculation methods will remain until these issues are addressed through more advanced techniques, such as robust implementation of the partition model and advanced predictive dose planning incorporating concepts such as biologic equivalent dose and dose volume histograms.[22]

A PRACTICAL APPROACH TO DOSIMETRY

With an understanding of the basic principles of activity and their relationship to compartmental dose, it becomes evident that there are three main objectives to optimizing activity: (1) ensure that the nontargeted dose to the lungs is within a safe margin, generally accepted as < 25 Gy in a single administration and < 50 Gy lifetime exposure; (2) minimize the dose to the nontumor compartment (utilizing the partition model equations), accepted as < 70 Gy to the noncompromised liver and < 40 Gy to the compromised liver; and (3) optimize (not maximize) the dose to the tumor based on the principles of partition dosimetry, such that in the case of glass microspheres, the targeted dose is in the range of 200 to 500 Gy, and for resin microspheres, the dose is in the range of 100 to 120 Gy.

Although the MIRD, partition, and BSA models calculate activity through different variables, a loose relationship (and concordance) can be observed in many clinical scenarios (Figure 2). Thus, based on our general experience, we adhere to the REBOC consensus statement to determine which method to apply (ie, use MIRD for glass and BSA for resin microspheres) and confirm that this falls within the range of compartmental dose utilizing the partition model as previously outlined when the T/N ratio and compartmental volumes can be determined. Activity modulation (increased or decreased overall activity administered) can be performed based on the limits of the partition model. Although this method can be time intensive and laborious, free calculators have become available to provide fast and efficient modeling (Figure 2).

There are several other factors that may affect target dose (primarily relating to compromised liver function leading to liver failure), including the following:

- **Previous or current systemic chemotherapy.** Patients being treated with radiosensitizing agents (ie, gemcitabine) need to be treated with caution with either dose reduction or temporary cessation of chemotherapy for several weeks before and after TARE to preclude overdose and radioembolization-induced liver disease (REILD). Antiangiogenic agents (ie, bevacizumab, ziv-aflibercept) should be held for approximately 4 weeks prior to angiography given their propensity to induce vasospasm and dissection and, ultimately, the inability to satisfactorily deliver the intended dose.
- **Previous hepatic treatment with external beam radiation/stereotactic ablative radiotherapy/proton beam.** The most accurate method of determining the dose to the liver and safety of delivery of radioembolic is to evaluate the dose-volume histograms from the prior radiotherapy. It is crucial that one does not surpass the maximum liver dose to minimize the risk of hepatic failure.
- **Previous radioembolization.** Use caution in patients being retreated with TARE, as they are at increased risk of REILD. A small retrospective study by Lam et al demonstrated that repeat TARE was an independent risk factor for REILD in a multivariate analysis, with two of eight patients (25%) dying from this complication.[10] Both patients with a fatal outcome had a history of hepatic resection and were heavily treated with systemic chemotherapy both before the first TARE procedure and between the first and second TARE procedures. Of note, patients retreated with Y-90 did demonstrate objective tumor responses. Refinements in personalized dosimetry may increase the safety margin while maintaining therapeutic response.[19]

SUMMARY

Despite the challenges relating to dosimetry, TARE has been demonstrated to be a safe and effective liver-directed therapy utilizing current technology and techniques. Phase 3 clinical trials, both already conducted and under enrollment, utilize these methods (predominantly BSA-derived strategies for resin-based microspheres and MIRD-based strategies for glass-based microspheres). With refinement in the techniques and potential evolution in the technology, the hope is that through a deeper understanding of TARE, we can develop even safer and more effective iterations, both in modeling and technology. ■

1. Brown KT, Do RK, Gonen M, et al. Randomized trial of hepatic artery embolization for hepatocellular carcinoma using doxorubicin-eluting microspheres compared with embolization with microspheres alone. J Clin Oncol. 2016;34:2046-2053.

2. Klass D, Owen D, Buczkowski A, et al. The effect of doxorubicin loading on response and toxicity with drug-eluting embolization in resectable hepatoma: a dose escalation study. Anticancer Res. 2014;34:3597-3606.

3. Bilbao JI, de Martino A, de Luis E, et al. Biocompatibility, inflammatory response, and recanalization characteristics of nonradioactive resin microspheres: histological findings. Cardiovasc Intervent Radiol. 2009;32:727-736.
4. Kritzinger J, Klass D, Ho S, et al. Hepatic embolotherapy in interventional oncology: technology, techniques, and applications. Clin Radiol. 2013;68:1-15.
5. Kennedy A, Nag S, Salem R, et al. Recommendations for radioembolization of hepatic malignancies using yttrium-90 microsphere brachytherapy: a consensus panel report from the radioembolization brachytherapy oncology consortium. Int J Radiat Oncol Biol Phys. 2007;68:13-23.
6. Hendlisz A, van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J Clin Oncol. 2010;28:3687-3694.
7. van Hazel GA, Heinemann V, Sharma NK, et al. SIRFLOX: randomized phase III trial comparing first-line mFOLFOX6 (plus or minus bevacizumab) versus mFOLFOX6 (plus or minus bevacizumab) plus selective internal radiation therapy in patients with metastatic colorectal cancer. J Clin Oncol. 2016;34:1723-1731.
8. Gulec SA, Mesoloras G, Stabin M. Dosimetric techniques in 90Y-microsphere therapy of liver cancer: the MIRD equations for dose calculations. J Nucl Med. 2006;47:1209-1211.
9. Hilgard P, Hamami M, Fouly AE, et al. Radioembolization with yttrium-90 glass microspheres in hepatocellular carcinoma: European experience on safety and long-term survival. Hepatology. 2010;52:1741-1749.
10. Lam MG, Louie JD, Iagaru AH, et al. Safety of repeated yttrium-90 radioembolization. Cardiovasc Intervent Radiol. 2013;36:1320-1328.
11. Abbott AM, Kim R, Hoffe SE, et al. Outcomes of Therasphere radioembolization for colorectal metastases. Clin Colorectal Cancer. 2015;14:146-153.
12. Ho S, Lau WY, Leung TW, et al. Partition model for estimating radiation doses from yttrium-90 microspheres in treating hepatic tumours. Eur J Nucl Med. 1996;23:947-952.
13. Ho S, Lau WY, Leung TW, et al. Clinical evaluation of the partition model for estimating radiation doses from yttrium-90 microspheres in the treatment of hepatic cancer. Eur J Nucl Med. 1997;24:293-298.
14. Kao YH, Tan EH, Ng CE, Goh SW. Clinical implications of the body surface area method versus partition model dosimetry for yttrium-90 radioembolization using resin microspheres: a technical review. Ann Nucl Med. 2011;25:455-461.
15. Lewandowski RJ, Minocha J, Memon K, et al. Sustained safety and efficacy of extended-shelf-life (90)Y glass microspheres: long-term follow-up in a 134-patient cohort. Eur J Nucl Med Mol Imaging. 2014;41:486-493.
16. Paprottka KJ, Lehner S, Fendler WP, et al. Reduced peri-procedural analgesia following replacement of water for injection (WFI) with glucose 5% (G5) solution as the infusion medium for 90 yttrium resin microspheres [published online ahead of print June 3, 2016]. J Nucl Med.
17. Mazzaferro V, Sposito C, Bhoori S, et al. Yttrium-90 radioembolization for intermediate-advanced hepatocellular carcinoma: a phase 2 study. Hepatology. 2013;57:1826-1837.
18. Garin E, Rolland Y, Edeline J, et al. Personalized dosimetry with intensification using 90Y-loaded glass microsphere radioembolization induces prolonged overall survival in hepatocellular carcinoma patients with portal vein thrombosis. J Nucl Med. 2015;56:339-346.
19. Sangro B. Liver function considerations for post-selective internal radiation therapy resection (hepatocellular carcinoma and metastatic colorectal cancer). Future Oncol. 2014;10(15 suppl):57-59.
20. Breedis C, Young G. The blood supply of neoplasms in the liver. Am J Pathol. 1954;30(5):969-77.
21. Spreafico C, Maccauro M, Mazzaferro V, Chiesa C. The dosimetric importance of the number of 90Y microspheres in liver transarterial radioembolization (TARE). Eur J Nucl Med Mol Imaging. 2014;41:634-638.
22. Alber M, Nusslin F. Tools for the analysis of dose optimization: I. Effect-volume histogram. Phys Med Biol. 2002;47:2451-2458.

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