A Multicenter Study on Observed Discrepancies Between Vendor-Stated and PET-Measured ^{90}Y Activities for Both Glass and Resin Microsphere Devices

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Dosimetry-guided treatment planning in selective internal radiation therapy relies on accurate and reproducible measurement of administered activity. This 4-center, 5-PET-device study compared the manufacturer-declared ^{90}Y activity in vials with quantitative ^{90}Y PET/CT assessment of the same vials. We compared ^{90}Y PET-measured activity (A_{PET}) for 56 ^{90}Y-labeled glass and 18 ^{90}Y-labeled resin microsphere vials with the calibrated activity specified by the manufacturer (A_M). Additionally, the same analysis was performed for 4 ^{90}Y-chloride vials. The mean A_{PET}/A_M ratio was 0.79 ± 0.04 (range, 0.71–0.89) for glass microspheres and 1.15 ± 0.06 (range, 1.05–1.25) for resin microspheres. The mean A_{PET}/A_M ratio for ^{90}Y-chloride vials was 1.00 ± 0.04 (range, 0.96–1.06). Thus, we found an average difference of 46% between glass and resin microsphere activity calibrations, whereas close agreement was found for chloride solutions. We expect that the reported discrepancies will promote further investigations to establish reliable and accurate patient dosimetry and dose–effect assessments.

Key Words: resin microspheres; glass microspheres; ^{90}Y; PET/CT; activity

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Selective internal radiation therapy (SIRT) with radioactive microspheres is an established liver-directed therapy for both primary liver cancer and liver metastases. Both ^{90}Y glass and resin microspheres are used globally; they are Food and Drug Administration–approved in the United States, and they received the CE (Conformitè Europëenne) mark in the European Union.

Considerable evidence of dose–effect relationships for both tumor and nontumor liver have been demonstrated for ^{90}Y SIRT (*1*). In particular, for glass microspheres, Garin et al. highlighted a dose–response relationship in a prospective randomized trial, which demonstrated that planned personalized dosimetry improves outcomes compared with standard single-compartment dosimetry for locally advanced hepatocellular carcinoma (*2*). Another area of investigation is focused on posttreatment SIRT dosimetry, which obviates most of the difficulties linked to the hypothesis that pretreatment imaging-based dosimetry is a robust surrogate of the actual delivered absorbed dose. In that respect, recent studies have suggested the benefit of ^{90}Y PET–based dosimetry in hepatocellular carcinoma or cholangiocarcinoma (*3,4*).

For reliable dosimetry-guided treatment planning and dose–effect assessment from pretherapy imaging–based absorbed dose estimates, the net administered activity of ^{90}Y microspheres should be accurately determined. Accurate assay of ^{90}Y, an almost pure β-emitter, using activity meters is challenging compared with other radionuclides commonly used in nuclear medicine procedures (*5*). (In this work, we adopted the term *activity meter* for the reentrant well-type ionization chamber that is calibrated to convert a measured ionization current to an activity; this device is also colloquially referred to as a dose calibrator in North America. We reserved the use of *dose* for the absorbed dose in units of Gy.) The specific geometry and material composition of the source and its container affects the spectrum of Bremsstrahlung photons, hence affecting the activity meter measurement.

^{90}Y PET imaging is also challenging because of the low true coincidence count rates associated with the low yield of positron emission (0.0032%). Despite this, there have been multiple reports demonstrating the quantification accuracy of ^{90}Y PET in phantom studies when using state-of-the-art time-of-flight scanners (*6–8*). It should be noted that almost all phantom studies to date have used ^{90}Y in the form of a chloride solution and not the microsphere devices themselves. Reasons may include the difficulty of suspending microspheres in a uniform distribution throughout a phantom compartment.

In this work, we used quantitative ^{90}Y PET/CT imaging to measure the ^{90}Y microsphere vial activity in air before SIRT with resin and glass microspheres at 4 institutions on 5 scanners: PET-1, a Biograph Vision 600 (Siemens Healthineers) at Lausanne University Hospital (Centre hospitalier universitaire vaudois [CHUV]); PET-2, a Discovery 690 (GE Healthcare) at CHUV; PET-3, a Biograph mCT 40 (Siemens Healthineers) at the University of Michigan; PET-4, a Biograph Vision 600 (Siemens Healthineers) at Luzerner Kantonsspital; and PET-5, a Biograph 40 mCT (Siemens Healthineers) at the University Hospital of Nantes. Additional data

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came from PET measurements of vials containing ^{90}Y in chloride solution and as a liquefied resin. We compared the PET-measured activity with the activity on the calibration certificate supplied by the vendor for each vial with appropriate decay correction.

MATERIALS AND METHODS

We analyzed ^{90}Y vials from 3 different manufacturers: 56 ^{90}Y-labeled glass microsphere vials (TheraSphere; Boston Scientific), 18 ^{90}Y-labeled resin microsphere vials (SIR-Spheres; Sirtex Medical), 4 vials containing ^{90}Y-chloride solution (2 from Curium and 2 from Eckert and Ziegler), and 1 vial containing a solution of dissolved ^{90}Y-labeled resin microspheres (liquefied resin). All vials were imaged in air at a single bed position centered on the 3 tomographic directions of the PET scanner to yield peak sensitivity.

Glass Microspheres

A first dataset of 43 ^{90}Y-labeled glass microsphere vials (0.7–6.3 GBq) was imaged on PET-1, with a subgroup of 8 of these vials (0.7–6.3 GBq) being additionally measured on PET-2. Another dataset of 13 glass microsphere vials (2.3–8.6 GBq) was imaged on PET-3.

Resin Microspheres

^{90}Y-labeled resin microsphere vials (3.3–4.6 GBq) were imaged on PET-1 (n = 11), PET-2 (n = 1), or PET-4 (n = 6).

Chloride Solution

In addition to performing acquisitions on microsphere vials, we acquired PET/CT data for vials of liquid ^{90}Y-chloride solution. Of these, 2 (0.4 and 2.5 GBq) were acquired on PET-1 and 2 (0.4 and 4.4 GBq) on PET-3.

Liquified Resin Microspheres

The vial with the solution of dissolved ^{90}Y-labeled resin microspheres was from a prior study evaluating the reliability of measuring ^{90}Y activity using PET performed at the University Hospital of Nantes in collaboration with the French National Standard Laboratory in Paris (LNHB [Laboratoire National Henri Becquerel]–CEA [Commissariat à l'énergie atomique et aux énergies alternatives]). For this purpose, a reference activity of resin microspheres (2.95 GBq) was first dissolved (*9*), measured using the triple- to double-coincidence ratio method with Cherenkov counting at LNHB-CEA, and then shipped to the University Hospital of Nantes for a PET/CT acquisition on PET-5.

PET/CT Reconstruction and Quantification

Supplemental Table 1 summarizes acquisition and reconstruction parameters for the different PET/CT devices (supplemental materials are available at http://jnm.snmjournals.org). Manufacturer-recommended reconstruction parameters were used for ^{90}Y. Considering the measurements on PET-1 and PET-4 (the 2 Biograph Vision 600 devices), we tested both absolute and relative scatter corrections available with the manufacturer software. The relatively high noise associated with low-count ^{90}Y PET can affect the scatter correction with relative scaling, and some bias can appear in the final quantification as reported previously (*6*). Since the preliminary quantitative assessment showed, as expected, no significant difference between the 2 scatter methods in the low-scatter setting (in air) of the current experiment (Supplemental Tables 2 and 3), we focus on results obtained with the absolute scatter correction.

In all PET scanners used in the current study, the software enables ^{90}Y quantitation automatically from the local ^{18}F system cross-calibration, accounting for the ^{90}Y specific physical decay and positron branching ratio. The quantitative PET data were decay-corrected to the start of the PET acquisition. On the PET images, we defined cylindric (50 mm in diameter, 5 cm high) volumes of interest that encompassed the vials (diameters of 25, 35, and 25 mm for resin, glass, and ^{90}Y-chloride, respectively), to minimize any signal loss due to partial-volume effects.

Manufacturer-Specified Activity Assessment

The manufacturer-specified calibrated activity was reported in a document shipped with the vial to the different hospitals. In this document, the manufacturer indicates the vial activity and the time of the calibration. After performing the manufacturer-specified procedure for establishing a local calibration factor, we routinely verified the activity by measuring the received vial in the local activity meter. Specifically, nominal manufacturer activity was used for resin microspheres, whereas the manufacturer-measured total activity (not nominal) was used for glass microspheres. The local versus certified manufacture activity was found to be within 5% at all centers.

Comparison of PET-Derived Activity with Manufacturer-Specified Value

For each measurement, the total PET activity measured in the vial volume of interest (A_{PET}) was compared with the vial activity reported in the manufacturer calibration sheet (A_M) decay-corrected to the start of the PET acquisition, using the ratio A_{PET}/A_M. We assessed for statistical differences in A_{PET}/A_M ratios for the same microsphere type obtained in different PET scanners by applying ANOVA and multiple-comparison tests using the MATLAB statistical toolbox (version R2021a; MathWorks). A significant difference was considered present for P values of less than 0.05.

RESULTS

Figure 1 shows a dot-plot representation of the A_{PET}/A_M distribution across all 4 vial types and all centers. Table 1 presents the

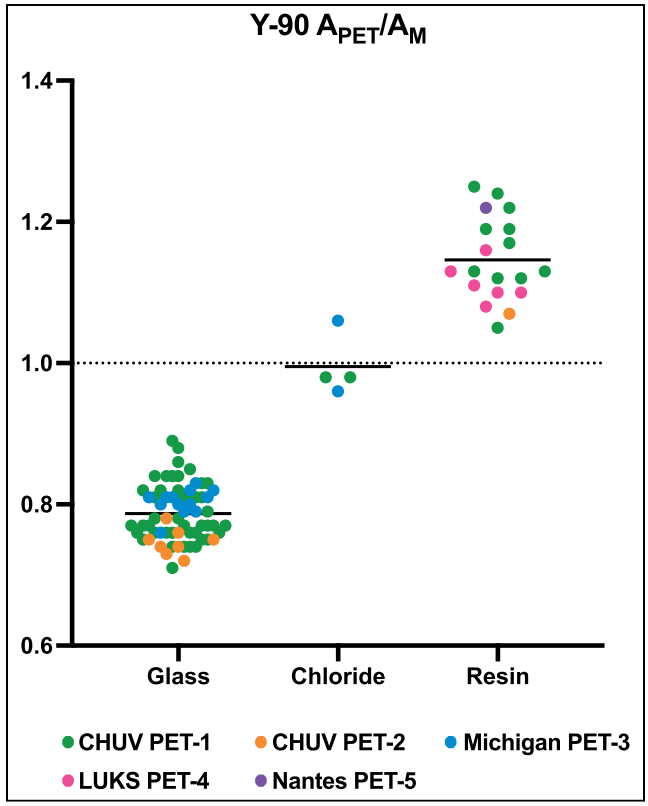

FIGURE 1. Distribution of A_{PET}/A_M ratios for the 4 vial products tested in this study (i.e., ^{90}Y-labeled glass microspheres, ^{90}Y-chloride solution, ^{90}Y-labeled resin microspheres, and ^{90}Y-labeled liquefied resin). LUKS = Luzerner Kantonsspital, the ^{90}Y-labeled liquefied resin (Nantes PET-5, purple dot) was associated to the resin's category.

TABLE 1
Summary of A_{PET}/A_M Results

Product	Manufacturer	Vials (*n*)	Scanner	A_{PET}/A_M		
				Mean	SD	Range
Glass	Boston Scientific	43	PET-1	0.79	0.04	0.71–0.89
Glass	Boston Scientific	8	PET-2	0.74	0.02	0.72–0.78
Glass	Boston Scientific	13	PET-3	0.80	0.02	0.76–0.83
Glass	Boston Scientific	64	All	0.79	0.04	0.71–0.89
Resin	Sirtex Medical	11	PET-1	1.16	0.06	1.05–1.25
Resin	Sirtex Medical	1	PET-2	1.07		
Resin	Sirtex Medical	6	PET-4	1.11	0.03	1.08–1.16
Resin	Sirtex Medical	18	All	1.15	0.06	1.05–1.25
Resin* liquified	Sirtex Medical	1	PET-5	1.22		
Chloride	Curium	2	PET-1	0.98	0.01	0.98–0.98
Chloride*	Eckert and Ziegler	2	PET-3	1.01	0.07	0.96–1.06
Chloride	All	4	All	1.00	0.04	0.96–1.06

*Data for which relative scatter correction was applied; otherwise, absolute scatter correction was applied.
Liquification was by LNHB-CEA.

summary statistics for all measurements (full data are available in Supplemental Presentation 1). The mean A_{PET}/A_M ratio for ^{90}Y glass spheres was 0.79 ± 0.04 (range, 0.71–0.89). No statistical differences in mean A_{PET}/A_M for ^{90}Y glass spheres were found between PET-1 and PET-3 ($P = 0.43$). Statistical differences were found between PET-1 and PET-2 ($P = 0.009$) and between PET-2 and PET-3 ($P = 0.002$). The mean A_{PET}/A_M ratio for the resin spheres was 1.15 ± 0.06 (range, 1.05–1.25). In this case, no statistical difference was found between PET-1 and PET-4 ($P = 0.072$).

The mean A_{PET}/A_M measured in ^{90}Y-chloride vials was 1.00 ± 0.04 (range, 0.96–1.06) (Table 1; Supplemental Table 4). The A_{PET}/A_M measured for the liquefied resin spheres in PET-5 was 1.22 ± 0.12, whereas good agreement was found between the LNHB-CEA reference activity and the PET activity measurements, with a ratio of 1.01.

DISCUSSION

In this study, we used PET as an independent measure of activity for ^{90}Y microsphere vials in air and compared this measure with the activity reported in the respective manufacturer's calibration sheet for ^{90}Y-labeled resin and glass microspheres and ^{90}Y in chloride solution and liquefied resin. Although we report substantial discrepancies for resin and glass microspheres, close agreement is reported for the chloride solution. Furthermore, PET measurement of the liquefied resin activity is in excellent agreement with the national metrology laboratory reference measurement, suggesting an accurate PET quantification.

For the resin spheres, we reported an average A_{PET}/A_M ratio of 1.15 ± 0.06 (i.e., A_M underestimates A_{PET} by 13%); this value is compatible with the high-purity germanium National Institute of Standards and Technology–referred results of Graves et al., who recently reported a ratio of 1.233 ± 0.030 (*10*). In addition, we provided original data for the glass spheres showing a trend opposite that of resin, an A_{PET}/A_M ratio of 0.79 ± 0.04 (i.e., A_M systematically overestimating A_{PET} by 27%). Therefore, a relative difference of about 46% exists between the 2 manufacturers' ^{90}Y activity calibrations; that is, 1 Bq of ^{90}Y measured in the activity reference frame of the glass microsphere manufacturer corresponds to 1.46 Bq in that of the resin microsphere manufacturer.

Quantitative PET imaging of ^{90}Y is challenging, but it is enhanced by the state-of-the-art time-of-flight systems used in this study. However, an error in the PET-reconstructed activity may arise from a potentially inaccurate attenuation correction due to inadequate modeling of higher-density materials such as glass. The glass containers for the ^{90}Y-chloride and resin microspheres have a minimal thickness. Such a thickness will have minor effects on PET-reconstructed activity. The following observations support this claim: first, our A_{PET}/A_M for resin microspheres is consistent with prior studies (*10,11*) reporting that A_M is underestimated using a measurement approach different from PET; second, our A_{PET}/A_M is near unity for ^{90}Y-chloride, for which activity meter measurements are well known with a traceable standard; and third, we obtained a near-unity value for the ratio of the LNHB-CEA reference activity to the PET activity, indicating the good agreement of the 2 methods (i.e., the coincidence Cherenkov counting and the PET) in estimating the vial activity. However, the combination of a thick glass V-Vial (Wheaton Industries, Inc.) bottom and glass microspheres settling at that bottom may lead to a combined glass thickness potentially great enough to introduce bias in the attenuation correction. To estimate the potential bias, we used cone-beam CT of a glass microsphere vial to create a high-resolution (0.1 mm) model of the geometry and material used in our study. Nominal linear attenuation coefficients were then assigned, and attenuation correction factors (ACFs) were calculated along a few lines of response. We compared ACFs from the high-resolution model with ACFs calculated from the CT-derived attenuation map used in the PET reconstruction. Assuming nominal values for diameter and total number of microspheres, with a packing ratio of 0.6, we estimated the potential ACF bias along

evaluated lines of response to vary from −11% to +13%. The average ACF bias was no greater than 6%, which would move our results only slightly toward unity, leaving the A_{PET}/A_M ratio at or below 0.85. The sensitivity of attenuation correction was also tested by increasing the CT numbers above 600 Hounsfield units by 20% and then performing PET reconstruction. The resulting activity concentration image had a maximum difference of 3.6%, demonstrating minimal sensitivity to changes in Hounsfield units.

Although primary measurements from national laboratories have been reported for both devices (*12,13*), any changes from the specific source and container tied to these measurements will impact the ^{90}Y Bremsstrahlung energy spectrum and thereby the activity meter assay. One study reported a systematic bias of 4% due to likely changes in the acrylic shield used by glass microspheres (*14*). Monte Carlo simulations that model the composition and geometry of the vials, as well as the devices, might provide more insight on their impact on both the PET measurement and activity meter calibration but are beyond the scope of this work.

To the best of our knowledge, we believe this is the first report of such observed differences for ^{90}Y glass microspheres between PET and vendor-stated activity. The purpose of this study is not to fully explain the discrepancies we have observed but to share our observations that suggest a significant bias when comparing PET quantification with vendor-stated activity for both glass and resin ^{90}Y microsphere devices. Such differences would likely not affect clinical practice given the large number of patients safely and effectively treated to date with activities as stated by the vendors. However, it is important from a metrological standpoint to know the activities administered to patients; reporting true activities should enable more accurate radiobiologic modeling and dosimetry comparisons across devices and modalities. For example, our results should be considered within the context of studies reporting a lower biologic effect per Gray for glass versus resin microspheres when treating the same hepatic disease (*15*).

CONCLUSION

We have presented original data comparing quantitative PET and manufacturer-declared total activity in ^{90}Y-labeled microspheres and ^{90}Y-chloride vials. Manufacturer-declared vial activities were substantially different when measured by quantitative PET for glass (mean ratio, 0.79) and resin (mean ratio, 1.15), which showed opposite trends with a large relative difference of 46% between them. In ^{90}Y-chloride vials, PET and manufacturer-declared activities agreed closely. We expect that the reported discrepancies will promote further investigations to establish reliable and accurate patient injected-activity measurement and thus consistent dosimetry and dose–effect relation assessments.

DISCLOSURE

Yuni Dewaraja acknowledges grant funding from NIH R01 EB022075. Maurizio Conti is full-time employee of Siemens Medical Solutions USA, Inc. No other potential conflict of interest relevant to this article was reported.

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KEY POINTS

QUESTION: How accurate are vendor-specified calibrated activities used for therapy and absorbed dose assessment in ^{90}Y SIRT?

PERTINENT FINDINGS: We compared quantitative ^{90}Y PET measurements against vendor-specified calibrated activities in both glass and resin microsphere vials across multiple centers and devices. We found a large difference between PET measurements and reported vial activities (average, −21% for glass and +15% for resin).

IMPLICATIONS FOR PATIENT CARE: Accounting for the observed differences can lead to a shift of reported administered activity and absorbed dose thresholds in dose–effect studies.

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