

# Radioembolization With Holmium-166 Polylactic Acid Microspheres: Distribution of Residual Activity in the Delivery Set and Outflow Dynamics During Planning and Treatment Procedures

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Robert Drescher, MD<sup>1</sup> , Philipp Seifert, MD<sup>1</sup> ,  
Falk Gühne, MD<sup>1</sup>, René Aschenbach, MD<sup>2</sup> ,  
Christian Kühnel, MSc<sup>1</sup>, and Martin Freesmeyer, MD<sup>1</sup> 

## Abstract

**Purpose:** To evaluate the microsphere outflow dynamics and residual Ho-166 activity during and after transarterial radioembolization planning and treatment procedures, and to assess the distribution and predilection sites of residual activity in the proprietary delivery set and the microcatheter. **Materials and Methods:** Fifteen planning and 12 therapeutic radioembolization procedures were performed with poly-L-lactic acid microspheres loaded with Ho-166. The amount and distribution of residual activity was assessed by dose calibrator measurements and SPECT imaging. The activity flow profile from the microcatheter was assessed dynamically. For planning procedures, different injection methods were evaluated in order to attempt to decrease the residual activity. **Results:** The median residual activities for planning and treatment procedures using standard injection methods were 31.2% (range 17.3%–44.1%) and 4.3% (range 3.5%–6.9%), respectively. Planning residual activities could be decreased significantly with 2 injection methods similar to treatment procedures, to 17.5% and 10.9%, respectively ( $P = 0.002$ ). Main predilection sites of residual microspheres were the 3-way stopcock and the outflow needle connector. During treatment procedures, more than 80% of the injected activity is transferred during the first 3 injection cycles. **Conclusion:** After treatment procedures with holmium-loaded microspheres, mean residual activity in the delivery set is reproducibly low and between reported values for glass and resin microspheres. The majority of microspheres is transferred to the patient during the second and third injection cycle. An estimated residual waste of 3% to 4% may be included in the treatment activity calculation. For planning procedures, a modified injection technique should be used to avoid high residual activities.

## Keywords

holmium, liver tumor, radioembolization, SIRT, TARE

## Introduction

Transarterial radioembolization is an interventional loco-regional treatment for primary and secondary liver malignancies.<sup>1</sup> Glass and resin microspheres loaded with yttrium-90, and poly-L-lactic acid (PLLA) microspheres loaded with holmium-166 are available. Potential advantages are the shorter half-life of Ho-166 (26.8 hours) compared with Y-90 (64.1 hours), its paramagnetic properties facilitating localization and quantification by magnetic resonance imaging (MRI), and better visibility by SPECT (single-photon emission computed tomography) due to its gamma radiation (81 keV peak, abundance 6.7%).<sup>2–4</sup>

As for resin and glass microspheres, a proprietary administration device is provided by the manufacturer for PLLA microspheres. This “delivery set” should be used for planning and treatment procedures. For PLLA microspheres, an option is to perform the planning procedure (holmium scout

<sup>1</sup>Clinic of Nuclear Medicine, Jena University Hospital, Jena, Germany

<sup>2</sup>Institute of Diagnostic and Interventional Radiology, Jena University Hospital, Jena, Germany

### Corresponding Author:

Martin Freesmeyer, MD, Clinic of Nuclear Medicine, Jena University Hospital, Am Klinikum 1, Jena 07747, Germany.

Email: martin.freesmeyer@med.uni-jena.de

dose, HSD) with the same type of microspheres used for radioembolization (RE) treatment instead of using Tc-99m macro-aggregated albumin (MAA), that are commonly used for glass and resin microsphere RE procedures.<sup>3</sup> The Ho-166 activity for a HSD procedure of the whole liver should not exceed 250 MBq Ho-166. The theoretical risk of extrahepatic tissue damage for this activity is low, which has been confirmed in 82 clinical procedures.<sup>5,6</sup> No adverse events related to extrahepatic depositions occurred after a median follow-up of 4 months.<sup>7</sup>

Knowledge about handling specificities of the delivery set, the flow dynamics during microsphere injection, and potential problems which may impair complete administration of the therapeutic activity to the patient are of importance to the interventionalist. For resin and glass microspheres, it has been shown that the majority is transferred at the beginning of a procedure, with the activity flow decreasing nearly exponentially with each flushing cycle. Mean residual activities in the application devices for resin and glass of 4.0% (median 3.6%, range 1.2%–6.6%) and 3.4% (median 3.4%, range 0.9%–8.8%), respectively, have been reported.<sup>8,9</sup> Residual activities of up to 17% may occur.<sup>10,11</sup>

The aim of this study was to evaluate the handling of the PLLA microspheres delivery set, the microsphere outflow dynamics during planning and treatment procedures, and to determine amount, variability and predilection sites of undelivered activity.

## Materials and Methods

All procedures were performed with Ho-166-loaded PLLA microspheres (QuiremSpheres, Terumo, Japan). Postprocedural measurements of residual activities and post- and periprocedural measurements of flow dynamics did not influence clinical decisions, conduct of the procedures and patient care. The prospective study was approved by the institutional review board (IRB) of the Jena University Hospital, Reg. No. 2020-1979.

### General Information on Holmium Radioembolization

Planning and treatment radioembolization of a whole liver with holmium-containing microspheres were devised to be performed with 3 and 30 million PLLA microspheres, respectively. This amount was shown to allow an accurate simulation of RE microsphere distribution and to contain an amount of holmium to be visible on MRI.<sup>12</sup> The microspheres are delivered in a vial (V-vial) in 2 mL of a resuspension medium, containing Pluronic F-68 (Sigma-Aldrich Chemie BV, The Netherlands) and phosphate buffer.<sup>13</sup> Calibration is done by the manufacturer so that the desired activity of Ho-166 in the V-vial is reached at the time of

injection. For the HSD, 2 standard vials of 80 MBq and 170 MBq Ho-166 are delivered, but up to 3 vials with personalized activities not exceeding a total of 250 MBq Ho-166 can be ordered (initial activities). For treatment, vials with 1 to 15 GBq Ho-166 can be ordered.<sup>14</sup>

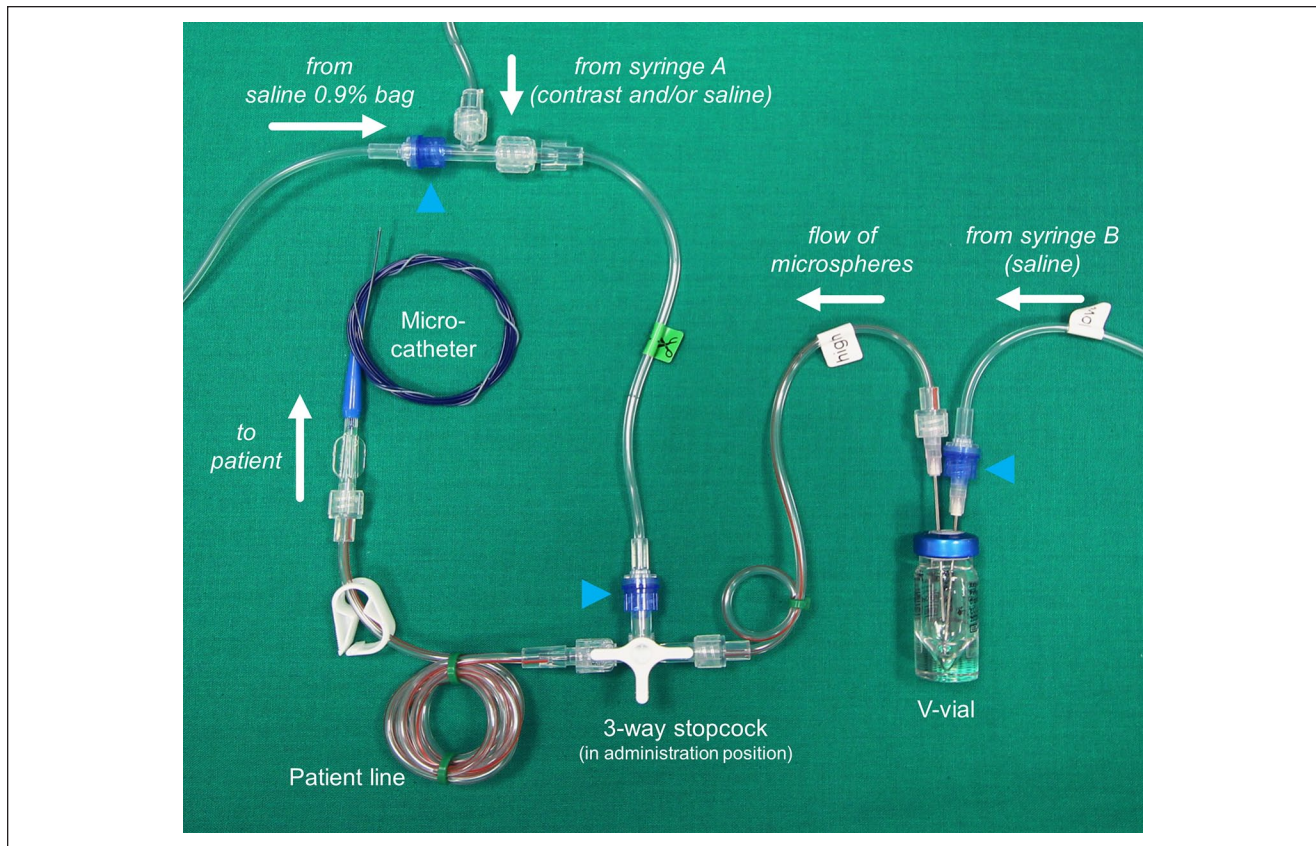
PLLA microspheres have a density of 1.4 g/mL. The weight of 1 million microspheres is 20 mg, the holmium content is 19% to 20%.<sup>3</sup> The specific activity of microspheres delivered for HSD (“QuiremScout”) is lower than that used for RE procedures (“QuiremSpheres”) due to different duration and intensity of neutron irradiation during production (4.2–4.7 MBq/mg and 11.6–15.3 MBq/mg, respectively, in this study). The median number of microspheres containing 1 GBq Ho-166 was 11.1 million (range 10.6–11.9 million) for HSD and 4.0 million (range 3.3–4.3 million) for RE procedures. The number of microspheres containing a certain Ho-166 activity was calculated based on the specific activity given for each vial of PLLA microspheres.

The delivery set consists of a tube line B (with syringe B) to inject 0.9% saline solution into the V-vial and to bring the microspheres into suspension, and a tube line A (with syringe A) leading from the V-vial through a 3-way stopcock, the patient line and the microcatheter to the patient (Figure 1). Microsphere administration is performed by manual injecting 0.9% saline solution into the V-vial with syringe A in a pulsed manner, with a recommended maximum flow rate of 5 mL/min and 0.1 mL per push.<sup>15</sup> To reach the maximum flow rate, a pressure of approximately 100 to 120 mm Hg is needed (our measurement). Application of contrast medium and flushing of patient line/microcatheter with 0.9% saline solution is possible with syringe B through the sidearm of the 3-way stopcock. The inner volume of the system between the efferent needle and the tip of the microcatheter is 3.2 mL (microsphere flow from V-vial to patient). For contrast media injection and flushing, the inner lumen between syringe A and the tip of the microcatheter is 4.3 mL, and between the 3-way stopcock and the tip of the microcatheter is 2.4 mL. The inner volume of the microcatheter itself is 0.6 mL. Setup of the delivery set is the same for planning and treatment procedures and was done strictly adhering to manufacturer recommendations.<sup>16</sup> Progreat 2.7 F/130 cm microcatheters (Terumo, Japan; inner diameter 0.025 inches) were used.

### Planning Procedures

Fifteen HSD procedures with initial activities from 69 MBq to 174 MBq Ho-166 were performed (Table 1). The first 2 procedures were in-patient planning procedures, the remaining procedures were performed ex vivo.

The standard method of injection of the HSD recommended by the manufacturer is to administer at least 20 mL saline solution from syringe B (4×5 mL), until the vial is



**Figure 1.** Poly-L-lactic acid (PLLA) microspheres delivery set. Saline solution injected with syringe B flushes the microspheres out of the V-vial, through the 3-way stopcock to the patient. The 5-mL syringes can be refilled from attached saline bags. Blue connectors (arrowheads) are 1-way valves.

visually empty. In order to attempt to decrease the residual activity and to improve microsphere outflow dynamics during the procedure, the standard injection method was compared with 2 alternative injection methods:

- Standard method, procedures 1–5: 6 cycles of 5 mL saline 0.9% through the V-vial from syringe B (30 mL in total),
- Alternative method A, procedures 6–10: 6 cycles of 5 mL saline 0.9% through the V-vial from syringe B (30 mL in total); after cycles 1 to 4, intermittent injection of 2.5 mL saline 0.9% from syringe A,
- Alternative method B, procedures 11–15: 8 cycles of 5 mL saline 0.9% through the V-vial syringe B (40 mL in total); after cycles 1 to 6, intermittent injection of 2.5 mL saline 0.9% from syringe A.
- Injections were performed pulsatile, with flow rates of 4 to 5 mL/min.

To evaluate application dynamics during *ex vivo* procedures, that is, to assess the proportion of activity transferred

with each injection cycle, the microcatheter tip was placed in a 10 mL collection tube for each cycle. Activity in the tubes was measured separately in a dose calibrator (ISOMED 2010, Nuvia Instruments, Germany), and the proportion per tube calculated in relation to the sum of all tubes.

### Treatment Procedures

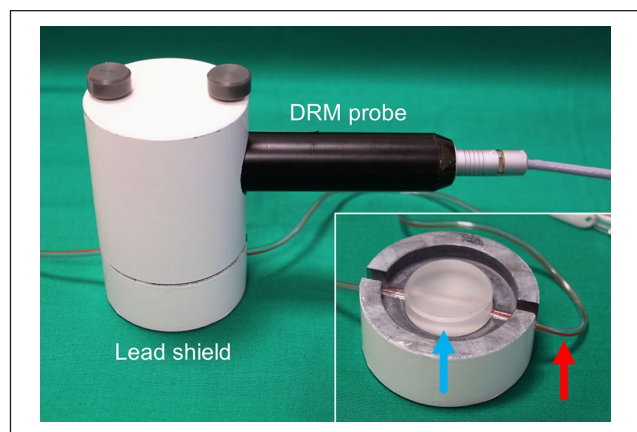
Twelve therapeutic, *in vivo* RE procedures with prescribed activities from 993 MBq to 4627 MBq Ho-166 (median 3105 MBq Ho-166) were performed. The median number of prescribed microspheres was 10.7 million (range 3.9–19.6 million). Injection was performed strictly adhering to manufacturer recommendations: 6 cycles of 2.5 mL saline 0.9% from syringe B alternating with 2.5 mL contrast agent and 5 mL saline 0.9% from syringe A (at least 5 cycles are recommended), followed by 20 mL from syringe B to flush vial and lines (4×5 mL).

To enable continuous measurements of activity flow during *in vivo* procedures, a shielded measurement chamber was constructed from a PLLA microspheres delivery shield,

**Table 1.** Planning Procedure Characteristics.

Procedures	Initial Activities		No. of Microspheres	Residual Activities			Delivery Set (%)	Method of Injection	Localization of High Activity Accumulations
	V-Vial (MBq)	V-Vial (Millions)		Total (MBq)	Total (%)	V-Vial (%)			
HSD-01	74	0.9	12.8	17.3	2.8	14.5	S	(not imaged)	
HSD-02	160	1.9	49.9	31.2	1.1	30.1	S	(not imaged)	
HSD-03	161	1.9	54.0	33.5	2.3	31.2	S	3-way stopcock	
HSD-04	85	1.0	37.4	44.1	3.0	41.1	S	microcatheter connector	
HSD-05	76	0.8	22.6	29.8	2.3	27.5	S	microcatheter connector, 3-way stopcock	
HSD-06	174	1.9	22.2	12.8	3.1	9.7	A	3-way stopcock	
HSD-07	74	0.8	9.7	13.1	3.6	9.4	A	3-way stopcock, V-vial	
HSD-08	169	2.0	40.2	23.8	2.6	21.2	A	3-way stopcock	
HSD-09	74	0.9	13.0	17.5	4.0	13.5	A	3-way stopcock	
HSD-10	84	0.9	18.4	22.1	2.5	19.6	A	3-way stopcock, microcatheter connector	
HSD-11	83	0.9	8.7	10.5	2.2	8.3	B	3-way stopcock, microcatheter connector	
HSD-12	69	0.8	7.6	10.9	5.5	5.5	B	V-vial, 3-way stopcock	
HSD-13	73	0.8	5.3	7.2	1.7	5.6	B	needle A connector, 3-way stopcock	
HSD-14	87	0.9	14.7	16.9	4.1	12.8	B	3-way stopcock	
HSD-15	169	1.9	24.6	14.5	4.9	9.6	B	V-vial, 3-way stopcock	

Abbreviations: S, standard injection method; A and B, alternative injection methods; HSD, holmium scout dose.



**Figure 2.** For measurement of activity flow during procedures, the patient line (red arrow) was placed between acrylic glass wafers (blue arrow) inside a lead shield with a dose rate meter (DRM) probe.

containing a scintillator probe (Automess 6150AD-18) attached to a dose rate meter (DRM; 6150AD, Automess GmbH, Ladenburg, Germany) (Figure 2). Readings in microsievert per hour were recorded in 1-second intervals. The sum of all dose rate readings per injection cycle divided by the sum of all cycles served as a surrogate to estimate the transferred activity per cycle (normalized to 60 seconds per cycle). The dynamic measurements described were carried out during 5 RE procedures (RE-08 to RE-12).

### Residual Activity Measurements and Imaging

After HSD and RE procedures, to avoid redistribution of residual activity the clamp at the patient line was closed, and the tip of the microcatheter was sealed with an adhesive transparent film. Activity distribution in delivery sets with microcatheters and vials was visually assessed on SPECT/CT fusion images (Symbia S gamma camera, Siemens Healthineers, Germany; parameters: duration 4 minutes, 32 time frames, 30 seconds per timeframe, 2 detectors, medium-energy low-penetration collimator, matrix 128×128, energy window 80 keV/15%, and Biograph mCT40 CT scanner, Siemens Healthineers, Germany; parameters: slice thickness 1.5 mm, tube voltage/current 80 kV/20 mAs). Imaging was performed after 14 of 16 HSD and after all RE procedures, respectively. Activity accumulations and their locations were noted, foci with the highest intensity were identified. After imaging, residual activities in the vial and in the remainder of the delivery set (with microcatheter) were measured separately in a dose calibrator (ISOMED 2010, Nuvia Instruments, Germany). All activity measurements were normalized to the starting time of the administration.

### Statistical Analysis

For statistical evaluation, p-values were calculated using the 2-sided Mann-Whitney *U* test for independent samples. Analyses of variance were performed to evaluate variance between more than 2 groups. Spearman's rho (correlation coefficient) calculations were carried out to evaluate correlations (SPSS Statistics, version 24, IBM Corp).

## Results

### Planning Procedures

No technical failures, for example, line/catheter blockages or leakages, occurred during the procedures. For the standard injection method, the median residual activity remaining in the delivery sets and V-vials was 31.2% (range 17.3%–44.1%) of the initial activity (Table 1). The median number of residual microspheres was 0.45 million (range 0.15–0.63 million). Using the alternative injection methods A and B, residual activities were significantly lower compared with method A, but still highly variable, from 7.2% to 23.8% (Table 2, power of analysis: 0.357). With all methods of injection, residual activity in the V-vials was significantly lower than in the delivery set (median 2.8%, range 1.1%–5.5% and median 13.5%, range 5.5%–41.1%, respectively;  $p < 0.001$ ). The high variability of residual activities was therefore caused by microspheres remaining in the delivery set.

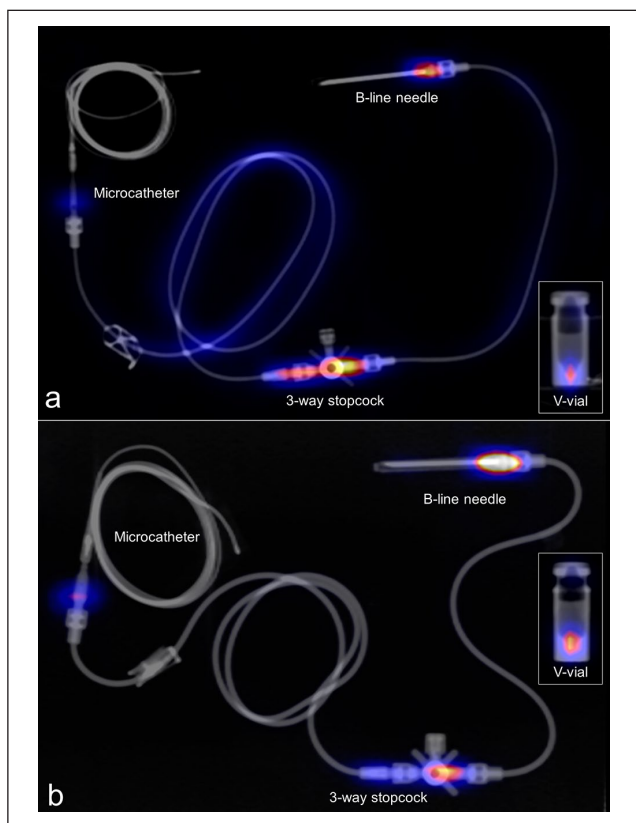
Thirteen delivery sets and V-vials were imaged. Residual activity in the V-vials was in all cases located only (7/13 procedures, 54%) or predominantly (6/13 procedures, 46%) at the bottom (Figure 3, insets). Visual predilection sites of microsphere accumulation were the connector of the outflow needle A at the V-vial, the microcatheter connector, the 3-way stopcock (junction between inflow and pivoting part) and the proximal end of the patient line close to the 3-way stopcock (Figures 3a and 4). On SPECT imaging, highest intensities were visualized at the 3-way stopcock (8/13 procedures, 62%) and at the microsphere connector (microcatheter side of the Luer lock, 2/13 procedures, 15%). After the procedure with the highest residual activity of 44% (HSD-04), a large activity accumulation was located at the microcatheter connector, distributing the adjacent lines (Figure 5). No backflow of activity into the inflow needle A or into the sidearm of the 3-way stopcock was identified.

Dynamic evaluations were performed during 9 ex vivo procedures and showed that with the standard injection method, the majority of the microspheres were transferred during the second half of the procedure, at injection cycles 4 and 5 (median 26%, range 10%–36% and median 31%, range 28%–37%, respectively) (Figure 6). Using alternative injection methods A/B, the majority of the microspheres

**Table 2.** Planning Procedures: Comparison of Different Methods of Injection.

Residual Activities	Method of Injection			p
	Standard	Alternative A	Alternative B	
Total (%) <sup>a</sup>	31.2 (17.3–44.1)	17.5 (12.8–23.8)	10.9 (7.2–16.9)	0.002
V-vial (%) <sup>a</sup>	2.3 (1.1–3.0)	3.1 (2.5–4.0)	4.1 (1.7–5.5)	0.184
Delivery set (%) <sup>a</sup>	30.1 (14.5–41.1)	13.5 (9.4–21.2)	8.3 (5.5–12.8)	0.001

<sup>a</sup>Values are presented as median (range).



**Figure 3.** SPECT/CT images of the delivery set and V-vial after planning (a, HSD-08) and treatment procedures (b, RE-09) show a similar pattern of residual activity. HSD, holmium scout dose; RE, radioembolization; SPECT, single-photon emission computed tomography.

were transferred during injection cycles 2 and 3 (median 45%, range 39%–55% and median 21%, range 9%–42%, respectively). Injection cycles 5/6 (method A) or 7/8 (method B), with a median transferred activity during these steps of 0.9% and 0.4%, therefore represent real flushing steps, aimed at emptying the delivery set.

### Treatment Procedures

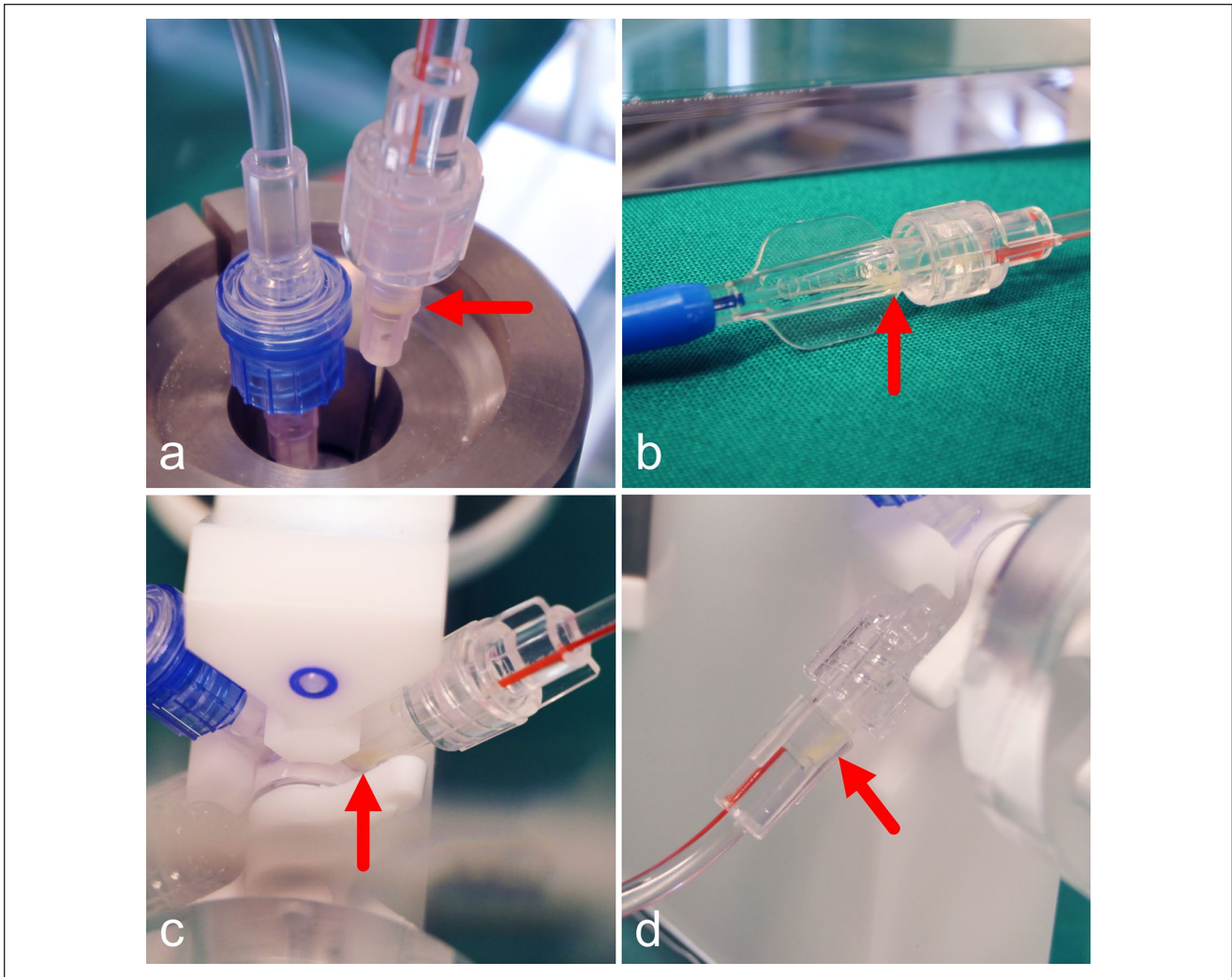
No technical failures occurred during the procedures. The median residual activity remaining in the delivery sets and V-vials was 4.3% (range 3.5%–6.9%) of the prescribed

activity (Table 3). The median number of residual microspheres was 0.52 million (range 0.27–0.77 million). A moderate negative correlation between relative residual activity and prescribed activity was evident ( $r_s = -0.718$ ;  $p = 0.009$ ). Absolute residual activities showed a strong positive correlation to prescribed activities ( $r_s = 0.755$ ;  $p = 0.005$ ). The lowest absolute residual activity was measured after the procedure with the lowest prescribed activity (RE-09, Table 3), representing the highest relative residual activity (6.9%).

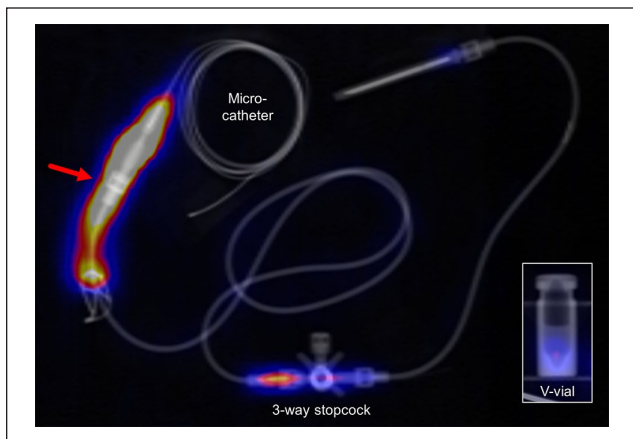
Residual activity in the V-vials was significantly lower than in the delivery sets (median 1.4%, range 0.2%–3.2% and median 3.4%, range 1.0%–5.3%, respectively;  $p < 0.001$ ). Contribution of V-vials and delivery sets toward the total residual activity was highly variable: After the 2 procedures with the lowest total residual activity of 3.5% (RE-03 and RE-10), proportion of these activities in the V-vials were 0.3% and 1.5%. After the 2 procedures with highest total residual activities of 6.7% and 6.9% (RE-08 and RE-09), proportions in the V-vials were 2.9% and 1.7%.

Visual predilection sites of microsphere accumulation after all procedures were the same as after HSD procedures: connector of the outflow needle A at the V-Vial, microcatheter connector (microcatheter side of the Luer lock), 3-way stopcock, and proximal end of the patient line (Figures 3b and 4). Focal spots with the highest intensities were visualized at the needle connector (9/12 procedures, 75%) and in the V-vial (3/12 procedures, 25%, Table 3). In one case, an additional focus of residual activity was seen in the line between needle A and 3-way stopcock (procedure RE-12). No backflow of activity into the inflow needle (from syringe B) or into the sidearm of the 3-way stopcock was identified. In the V-vials residual activity was located at the bottom (4/12 procedures, 33%), predominantly at the bottom (6/12 procedures, 50%, including procedure RE-07 with the highest residual V-vial activity), or predominantly at the top (2/12 procedures, 17%).

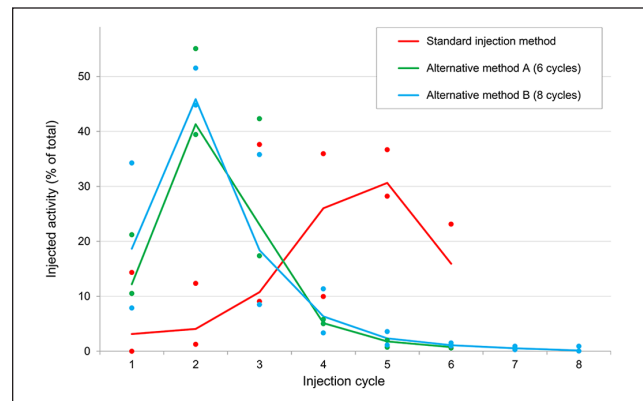
Dynamic evaluations showed that the majority of the microspheres were transferred through the patient line at the beginning of the procedure (Table 4). After the first 2 injection cycles, more than 60% (range 61%–71%), after the first 3 injection cycles, more than 80% (range 85%–92%) were transferred. Less than 3% were transferred during the sixth injection cycle and the final flushing combined (range 1.6%–2.3%).



**Figure 4.** Microsphere accumulations at the outflow needle connector (a), the microcatheter connector (b), the 3-way stopcock (c, junction between inflow and pivoting part), and the proximal end of the patient line (d, red arrows).



**Figure 5.** Planning procedure with the highest residual activity, 44.1% of 84.9 MBq Ho-166, performed with the standard injection method (HSD-04). The majority of the residual microspheres is located at the microcatheter connector (arrow). HSD, holmium scout dose



**Figure 6.** Planning procedures, transfer of activity during injection cycles. With the standard injection method, most microspheres are transferred during the second half of the procedure. Alternative injection methods A and B, only differing in the number of cycles, activity transfer is as expected for a suspension with continuous dilution. Curves represent median values, dots indicate ranges.

**Table 3.** Treatment Procedure Characteristics.

Procedures	Prescribed Activities		No. of Microspheres		Residual Activities			Localization of High Activity Accumulations
	V-Vial (MBq)	V-Vial (MBq)	V-Vial (Millions)	Total (MBq)	Total (%)	V-Vial (%)	Delivery Set (%)	
RE-01	3230		13.7	142.0	4.4	1.0	3.4	Needle A connector
RE-02	4544		19.6	178.6	3.9	0.2	3.8	Needle A connector, microcatheter connector
RE-03	3347		13.8	117.6	3.5	0.3	3.2	Needle A connector, 3-way stopcock
RE-04	4627		15.1	170.0	3.7	0.9	2.7	Needle A connector
RE-05	2980		10.6	175.4	5.9	1.4	4.5	Needle A connector, microcatheter connector
RE-06	2021		7.2	83.7	4.1	1.4	2.7	Needle A connector
RE-07	3800		16.0	157.9	4.2	3.2	1.0	V-vial
RE-08	2305		9.0	155.5	6.7	2.9	3.9	V-vial
RE-09	993		3.9	68.7	6.9	1.7	5.3	Needle A connector, 3-way stopcock
RE-10	3254		10.7	113.3	3.5	1.5	2.0	V-vial, 3-way stopcock
RE-11	2013		8.3	116.6	5.8	2.1	3.7	Needle A connector, V-vial
RE-12	1690		6.9	79.5	4.7	1.3	3.4	Needle A connector

Abbreviation: RE, radioembolization.



**Table 4.** Treatment Procedures: Activity Transfer per Injection Cycle.

Injection Cycle	Proportion of Injected Activity (%)		
	Median	Minimum	Maximum
1	23.5	21.1	26.9
2	40.9	37.3	49.8
3	23.2	14.4	27.7
4	7.7	4.4	9.9
5	3.0	1.8	3.7
6	1.2	1.2	1.5
Flush (4×5 mL)	0.8	0.4	0.9

### Technical Considerations

The PLLA microspheres delivery set is similar to the resin microspheres administration device: Injection is done from 2 syringes (microsphere administration and flushing/contrast media application), between which can be chosen by a 3-way stopcock, operated by a dial (Figure 1). In contrast, the construction of the glass microspheres administration device is simpler, with only one syringe and no 3-way stopcock, because no intermittent flushing or contrast application is done during the procedure.<sup>9</sup> Priming should be done slowly to prevent the formation of small air bubbles in the lines which are difficult to flush out. Residual air bubbles tended to accumulate at the sidearm of the 3-way stopcock (blue) and at the tube line A tee connector (Figure 1). During the procedure, arterial flow is visualized intermittently by injecting contrast media, allowing the interventionalist to immediately adapt the injection rate in case of flow reduction or stasis.

### Discussion

In previous studies evaluating RE with Ho-166 and introducing it into clinical practice, different injection methods and delivery sets were used. In an early feasibility study, microspheres were injected through a custom-made delivery set by injecting 15 to 20 mL of saline solution.<sup>17</sup> At that time, no proprietary delivery set for PLLA microspheres was available. In a later animal study and in the HEPAR I dose escalation study, pulsatile injection was done with a contrast media/saline mixture to provide constant control over the microsphere flow.<sup>12,18,19</sup> Currently, the manufacturer recommends to flush PLLA microspheres from the vial with saline solution, with intermittent injection of contrast media to check the arterial flow, through a proprietary delivery set.<sup>14,16</sup>

In a study comparing the prediction of lung shunting by HSD and MAA, the same injection method as in the HEPAR I dose escalation study with a mixture of contrast media/saline was used, but no residual activity values are reported.<sup>6</sup>

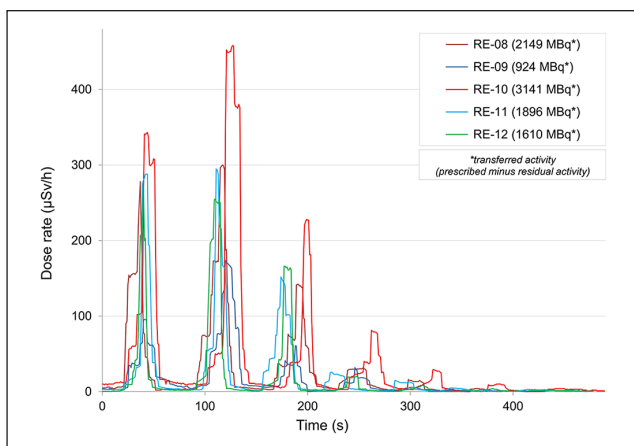
In the HSD safety study a mean residual activity of 8.7% was detected (prescribed activities 105–326 MBq Ho-166; administered activities 103–313 MBq Ho-166).<sup>7</sup> In the mentioned studies, injections were performed with 2.4 F or 2.7 F microcatheters (Progreat, Terumo, Japan).<sup>4</sup>

The standard injection method for HSD procedures as recommended by the manufacturer, means that injection is done solely through the V-vial.<sup>15</sup> Surprisingly, after the first 2 HSD procedures performed with this technique in our institution, we detected very high residual activities of 17.3% and 31.2% in the delivery sets (HSD-01 and HSD-02, Table 1). Further ex vivo evaluations performed with the simplified injection method showed even higher residual activities of up to 44.1% (HSD-04). Incomplete administration of the HSD may impair visualization of activity distribution in the liver. Absolute quantification would probably be impaired. Furthermore, ex vivo evaluation showed that relevant proportions of the microspheres were transferred during late injection cycles, at a point when the interventionalist may assume that he is just flushing lines and catheters before removal (Figure 6, standard method).

With alternative methods involving intermittent flushing from syringe A, residual activity in the delivery sets could be decreased significantly (alternative methods A/B; Table 2). Application dynamics was improved: The majority of microspheres was transferred during the first injection cycles, and low activity was transferred during flushing at the end of the procedure (Figure 6).

After RE procedures with PLLA microspheres evaluated in this study, using the injection method proposed by the manufacturer, a median relative residual activity of 4.3% was detected, ranging from 3.5% to 6.9% (mean  $4.8\% \pm 1.2\%$ ). These findings are similar to those measured after procedures with resin (4.0%, range 1.2%–6.6%) and glass microspheres (3.4%, range 0.9%–8.8%). Compared with resin and glass, the residual activity was less variable.<sup>8</sup> In the HEPAR I study, a mean residual activity of 6.1% was recorded, but the complete injection process was done with a mixture of contrast media/saline.<sup>19</sup> That study also found that relative residual activity was lower in the groups receiving the highest prescribed activities. In the phase II study evaluating Ho-166 microspheres for treatment of liver metastases in 38 patients, a median of 96% (range 41%–99%) of the prescribed activity was injected. The injection method is not described in detail. It is mentioned that in some cases, stasis occurred or infusion was stopped because of pain.<sup>20</sup>

Our measurements revealed a moderate negative correlation between initial/prescribed activity and relative residual activity, but no definite upper limit (saturation) of absolute residual activity could be identified. Taking the number of microspheres instead of the Ho-166 activity into account, about 10-fold more microspheres were used for treatment than for planning procedures (median: 10.67



**Figure 7.** Flow of activity measured at the patient line during five treatment procedures. Most microspheres are transferred during the first and second injection cycles. Less than 1% of the total activity is transferred during final flushing. Median procedure duration was 7:48 minutes (range 7:11–8:09 minutes).

million and 0.90 million, respectively), but the number of residual microspheres was only 2-fold higher (median 0.52 million and 0.20 million, respectively). This suggests that a limited number of microspheres gets stuck at the predilection sites, which represent irregularities at the inner surface of lines and catheters, but the high variability in the proportion of residual microspheres does not allow a prospective estimation.

Evaluation of infusion dynamics showed that in all RE procedures, more than 80% of the activity is transferred to the patient during the first 3 injection cycles (Figure 7). This dynamic profile is similar to resin microsphere and slower than glass microsphere injection. With neither microsphere type, treatment at more than one catheter position from one V-vial should be done, because microsphere transfer and distribution would not be predictable.

Predilection sites in the delivery sets for residual microspheres were the same for planning and treatment procedures. The 3-way stopcock and the needle A connector were the sites of the most intense activity accumulations (Figure 3). Apparent microsphere accumulations at the microcatheter connector (Figure 3b) were reduced by positioning it at a downward angle instead of horizontally, while the length of the patient line remained horizontally. The accumulations of microspheres in the proximal part of the patient line (Figure 3d) were seen to decrease when injecting with syringe A through the sidearm of the stopcock, with the saline flow coming from the side swirling away the microspheres stuck at this location. As with glass microspheres, in this study variable amounts of activity remained at the microcatheter connector after every procedure, emphasizing the recommendation that the delivery set and catheter should be disposed of without disconnection.<sup>9</sup>

Treatment from different vascular positions with the same microcatheter should be avoided.

All predilection sites of microsphere accumulation correspond to irregularities/steps at the inner surface of lines and catheters, at the Luer lock connection of 2 parts or at the rotating part of the 3-way stopcock. In a delivery set which is not assembled from different parts, but manufactured as one system avoiding these irregularities, low residual activities can be expected. A dedicated delivery set only for planning procedures may be simpler, without the 3-way stopcock and an optimized Luer lock connector for the microcatheter.

At the beginning of injecting into the V-vial, it sometimes took several pushes to bring the microspheres into suspension, due to their tendency to stick together at the bottom of the vial. The time period between the final production step and the procedure may be 1–3 days, during which the microspheres are not resuspended. As for glass microspheres, which are delivered in patient-specific doses, we recommend swiveling and tilting of the V-vial several times while it remains in the lead/acrylic container used for delivery. This problem does not arise with resin microspheres, since the patient-specific dose is prepared on-site usually on treatment day. The microspheres do not have time to agglutinate on the bottom of the vial. In this study, there was no evidence of adhesion of microspheres to the rubber septa after swiveling as a possible reason for abnormally high residual activities in V-vials. The beveled aspects of the needles, which have a higher diameter than those used in resin or glass microsphere administration devices (1.2 mm, 0.8 mm, and 0.9 mm, respectively), should face away from the inner V-vial surface to facilitate unhindered microsphere outflow.

Limitations of the study include the small number of procedures, particularly regarding planning procedures. Not all dose sizes could be tested with all injection methods. Only one type of microcatheter was used for all procedures. Different types may impact residual activity at the microcatheter connector. Influences by different operators and different microcatheters were not evaluated. To minimize influences of the pressure difference between the artery of a patient and a collection beaker for planning procedures, all injections were performed by the same physician keeping the flow rate as steady as possible.

In conclusion, the proprietary delivery set for PLLA microspheres is technically feasible. For planning procedures, completeness and reproducibility of microsphere transfer to the patient may be unfavorable when using the standard injection method. An injection technique resembling the method used for treatment procedures should be used. For treatment procedures, the recommended injection method leads to comparably low residual activities in the delivery sets. Inclusion of an estimated residual waste of 3%–4% in the calculation of the prescribed activity appears

to increase treatment accuracy, and to avoid undertreatment. As with delivery sets for resin and glass microspheres, constructional changes of the PLLA microspheres delivery set, focusing on the needle/microcatheter connectors and 3-way stopcock, would help to reduce residual activities and ensure consistent application of the prescribed activity to the patient.

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### ORCID iDs

Robert Drescher  <https://orcid.org/0000-0003-1890-3294>

Philipp Seifert  <https://orcid.org/0000-0002-3447-4971>

René Aschenbach  <https://orcid.org/0000-0003-3775-0449>

Martin Freesmeyer  <https://orcid.org/0000-0002-6462-3851>

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