Management of High Hepatopulmonary Shunting in Patients Undergoing Hepatic Radioembolization

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ABSTRACT

Purpose: To review the safety of hepatic radioembolization (RE) in patients with high (≥ 10%) hepatopulmonary shunt fraction (HPSF) using various prophylactic techniques.

Materials and Methods: A review was conducted of 409 patients who underwent technetium 99m–labeled macroaggregated albumin scintigraphy before planned RE. Estimated pulmonary absorbed radiation doses based on scintigraphy and hepatic administered activity were calculated. Outcomes from dose reductions and adjunctive catheter-based prophylactic techniques used to reduce lung exposure were assessed.

Results: There were 80 patients with HPSF ≥ 10% who received RE treatment (41 resin microspheres for metastases, 39 glass microspheres for hepatocellular carcinoma). Resin microspheres were used in 17 patients according to consensus guideline–recommended dose reduction; 38 patients received no dose reduction because the expected lung dose was < 30 Gy. Prophylactic techniques were used in 25 patients (with expected lung dose ≤ 74 Gy), including hepatic vein balloon occlusion, variceal embolization, or bland arterial embolization before, during, or after RE delivery. Repeated scintigraphy after prophylactic techniques to reduce HPSF in seven patients demonstrated a median change of –40% (range, +32 to –69%). Delayed pneumonitis developed in two patients, possibly related to radiation recall after chemoembolization. Response was lower in patients treated with resin spheres with dose reduction, with an objective response rate of 13% and disease control rate of 47% compared with 56% and 94%, respectively, without dose reduction (P = .023, P = .006).

Conclusions: Dose reduction recommendations for HPSF may compromise efficacy. Excessive shunting can be reduced by prophylactic catheter-based techniques, which may improve the safety of performing RE in patients with high HPSF.

ABBREVIATIONS

HCC = hepatocellular carcinoma, HPSF = hepatopulmonary shunt fraction, HVTT = hepatic vein tumor thrombus, MIRD = medical internal radiation dose, PVA = polyvinyl alcohol, PVTT = portal vein tumor thrombus, RE = radioembolization, RP = radiation pneumonitis, 99mTc-MAA = technetium 99m–labeled macroaggregated albumin, 90Y = yttrium-90

Complications and toxicities after yttrium-90 (90Y) radioembolization (RE) can result from nontarget deposition of microspheres, such as RE-induced liver disease from deposition in functional liver, ulceration from deposition in the stomach or bowel, and radiation pneumonitis (RP) from deposition in the lungs via hepatopulmonary shunting (1). Pathologic arteriovenous communications (arterioportal and arteriohepatic venous) are common in liver tumors (2,3). Microspheres injected into the hepatic artery can pass through arteriovenous shunts > 30 μm
in luminal diameter, traverse the heart, and lodge in pulmonary arterioles. In addition, in patients with portal hypertension and varices, microspheres can pass through arterioporal shunts, exit the liver via hepatofugal portal flow, traverse varices into a systemic vein, and then lodge in the lungs. These hepatopulmonary shunts can lead to clinically significant RP (4).

Hepatopulmonary shunting is measured by whole-body planar scintigraphy after injection of technetium 99m–labeled macroaggregated albumin ($^{99m}$Tc-MAA) into a hepatic artery to simulate future $^{90}$Y microsphere body planar scintigraphy after injection of technetium ($^{99m}$Tc). The purpose of our study was to review the safety and efficacy of performing RE on patients with high HPSF should undergo RE with reduction of administered activity or should not undergo RE at all (6,7). The purpose of our study was to review the safety and efficacy of performing RE on patients with high HPSF ($\geq$ 10%) with the use of prophylactic dose reduction or catheter-based shunt mitigation techniques or both.

**MATERIALS AND METHODS**

**Patients**

Institutional review board approval was obtained for this retrospective study. All data were handled in compliance with the Health Insurance Portability and Accountability Act. Between 2004 and 2014, 409 patients who underwent $^{99m}$Tc-MAA scintigraphy (Jubilant DraxImage, Kirkland, Quebec, Canada) before planned RE for primary or metastatic hepatic neoplasms at a single center were reviewed. Combined with prescribed and administered $^{90}$Y activities, HPSF was used to calculate expected absorbed dose to the lungs for each patient. Tumor cell type, presence of portal vein tumor thrombus (PVTT) or hepatic vein tumor thrombus (HVTT), and history of previous liver-directed therapies (ie, resection, transarterial chemoembolization, and percutaneous or laparoscopic ablation) were recorded. Of patients, 15 underwent $^{99m}$Tc-MAA scintigraphy but did not receive RE treatment; 394 patients received RE treatment. Retrospective analysis was performed of 80 high-risk patients treated with RE with HPSF $\geq$ 10% (median, 14.1%; range, 10%-54%) (Table 1).

The different methods to address elevated HPSF in these 80 patients (68% male; mean age, 64 y $\pm$ 12; cell type, hepatocellular carcinoma [HCC] 45%, other 55%; microspheres used, glass 49%, resin 51%) were reviewed. Patients were divided into three groups (Fig 1). The first group consisted of 17 patients treated earlier who received resin microspheres with administered activity reduced by 20%-40%, in adherence to published guidelines (SIR-Spheres yttrium-90 microspheres [package insert] Lane Cove, Australia: Sirtex Medical, Ltd, 2004.). The second group consisted of 38 patients in whom the expected single-administration lung dose was less than 30 Gy and the cumulative lung dose was less than 50 Gy, and no dose reductions or prophylactic interventions were performed. Expected lung doses were calculated from administered activity, HPSF, and medical internal radiation dose (MIRD) formulas based on estimated mass of lung tissue including blood being 1 kg (8). The third group consisted of 25 patients who underwent prophylactic catheter-based techniques to decrease HPSF. Five patients treated with prophylactic interventions also had dose reduction.

**Table 1. Demographics of 80 Patients with HPSF > 10% Treated by $^{90}$Y RE**

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n or Mean</th>
<th>SD or %</th>
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<tbody>
<tr>
<td>Age</td>
<td>64</td>
<td>$\pm$ 12</td>
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<tr>
<td>Male-to-female ratio</td>
<td>54:26</td>
<td>68%/32%</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
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<tr>
<td>HCC</td>
<td>36</td>
<td>45%</td>
</tr>
<tr>
<td>Metastatic colorectal carcinoma</td>
<td>17</td>
<td>21%</td>
</tr>
<tr>
<td>Metastatic neuroendocrine tumor</td>
<td>9</td>
<td>11%</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>5</td>
<td>6%</td>
</tr>
<tr>
<td>Metastatic renal cell carcinoma</td>
<td>4</td>
<td>5%</td>
</tr>
<tr>
<td>Other</td>
<td>9</td>
<td>11%</td>
</tr>
<tr>
<td>Macrovascular invasion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HVTT</td>
<td>4</td>
<td>5%</td>
</tr>
<tr>
<td>PVTT</td>
<td>20</td>
<td>25%</td>
</tr>
<tr>
<td>Previous treatment before RE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior transarterial chemoembolization</td>
<td>15</td>
<td>19%</td>
</tr>
<tr>
<td>Prior ablation</td>
<td>3</td>
<td>4%</td>
</tr>
<tr>
<td>$^{90}$Y microsphere treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glass</td>
<td>39</td>
<td>49%</td>
</tr>
<tr>
<td>Resin</td>
<td>41</td>
<td>51%</td>
</tr>
</tbody>
</table>

HCC = hepatocellular carcinoma; HPSF = hepatopulmonary shunt fraction; HVTT = hepatic vein tumor thrombus; PVTT = portal vein tumor thrombus; RE = radioembolization; $^{90}$Y = yttrium-90.

**Catheter-Based Shunt Reduction Techniques**

Prophylactic catheter-based techniques used in attempts to mitigate shunting included temporary hepatic vein balloon occlusion (9), bland arterial embolization preemptively or immediately after RE administration, and portosystemic variceal embolization. One or more techniques with or without dose reduction were used depending on clinical practice at the time, expected lung absorbed dose, and angiographic findings. Temporary hepatic vein balloon occlusion was used in eight patients. Dominant venous drainage was identified on imaging performed before the procedure and confirmed by early hepatic vein enhancement on cone-beam C-arm computed tomography (CT). To match the diameter of the draining veins, compliant balloons up to 14 mm diameter (Python; Applied Medical Resources Corp, Rancho Santa Margarita, California)
or valvuloplasty balloons up to 30 mm diameter (TYSHAK; B. Braun Interventional Systems, Inc, Bethlehem, Pennsylvania) were used. Balloons were introduced via the right internal jugular vein or femoral vein, inflated with dilute contrast material to low pressure (< 2 atm) immediately before ⁹⁰⁰Y administration, and kept inflated for 15 minutes after completion of administration (Fig 2a). No anticoagulation was administered.

Preemptive bland arterial embolization was performed on four patients with prominent arteriovenous shunting on the day of ⁹⁰⁰Y administration, using spherical (Embospheres [300–500 μm, n = 2; 500–700 μm, n = 1]; Merit Medical Systems, South Jordan, Utah) or particulate embolic agents (polyvinyl alcohol [PVA; 1,000–1,400 μm]; Cook, Inc, Bloomington, Indiana). Scintigraphy was repeated before administration of ⁹⁰⁰Y microspheres. In another patient, preemptive transarterial chemoembolization was performed, followed by repeated scintigraphy and RE treatment 5 weeks later.

In the four patients who received preemptive bland arterial embolization, one patient who received transarterial chemoembolization, and an additional 12 patients, bland arterial embolization was performed immediately after administration of ⁹⁰⁰Y (Fig 2b). The celiac axis was selected using an introducer guide (7-F RDC; Cordis Corp, Warren, New Jersey), and two parallel microcatheters were placed (Progreat Omega; Terumo Medical Corporation, Somerset, New Jersey; and Renegade HI-FLO; Boston Scientific, Marlborough, Massachusetts) with the ⁹⁰⁰Y microcatheter tip slightly distal to the bland arterial embolization microcatheter tip. For glass microspheres, only one 20-mL flush of the V-vial was performed, instead of the standard three flushes. Likewise for resin, only one 20-mL water or 5% dextrose flush and one air flush were performed. Immediately after visible passage of microspheres through the transparent delivery system tubing, concentrated bland arterial embolization material suspended in contrast medium was rapidly injected via the other microcatheter until stasis was achieved. Different embolic materials tested included 1-mm cubed gelatin foam slurry (SURGIFOAM [n = 1]; Ethicon, Inc, Cincinnati, Ohio), particle embolic agents (PVA [90–180 μm; n = 2], spherical embolic agents (Embospheres [100–300 μm, n = 3; 500–700 μm, n = 7; 500–700 μm, n = 1], and N-butyl cyanoacrylate glue with ethiodized oil (Histoacryl; Aesculap, Inc, Center Valley, Pennsylvania, or Lipiodol; Guerbet, Villepinte, France; n = 1) (Fig 2c). Delivered activity was calculated by subtracting residual activity from the initial total activity. Two patients had bland arterial embolization and hepatic vein balloon occlusion.

Preemptive variceal embolization was performed in two patients in whom arteriography demonstrated arterioportal shunting, hepatofugal portal flow, and drainage through portosystemic varices. Embolization with coils (Nester; Cook, Inc) of the right adrenal vein in one patient and the coronary vein in the other patient was performed (Fig 2d, e). ⁹⁹ᵐTc-MAA scintigraphy was
repeated immediately, followed by RE treatment; one patient was treated with immediate bland arterial embolization because of persistent arterioportal shunting into nontargeted liver.

Follow-up included clinical evaluation with physical examination at 4 weeks and 12 weeks and cross-sectional imaging at 10–12 weeks. To study the effect of dose reduction on efficacy in patients treated with resin microspheres, objective radiographic response, defined as either a complete response or a partial response, and disease control rate, defined as complete response + partial response + stable disease according to Response Evaluation Criteria in Solid Tumors (version 1.1), were assessed (10). One author (T.J.W.), blinded to intervention or dose reduction, reviewed all images. When comparing response rates, the five patients treated with catheter interventions and dose reductions were included in the dose reduction group. Respiratory complications including RP were the primary toxicity outcome of interest, graded according to the Common Terminology Criteria for Adverse Events (version 4.03) (11). RP was diagnosed based on radiographic and clinical criteria, including peribronchovascular consolidation and a restrictive ventilatory pattern on pulmonary function tests without evidence of active infection. Surviving patients with residual or recurrent disease typically proceeded to other treatment options, such as systemic chemotherapy or transarterial chemoembolization.

**Statistical Analysis**

Descriptive data are presented as mean and SD (normal) or median and range (nonnormal). Categorical data are
presented as percentages and counts. Pearson correlation and stepwise multiple linear regression analyses were performed to evaluate risk factors (pathology, HVTT, PVTT, liver-directed therapy) for elevated HPSF. For comparison between groups, Fisher exact test (categorical variables) was used. A P value of < .05 was considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics for Windows version 20.0 (IBM Corporation, Armonk, New York).

RESULTS
Of 409 patients who underwent HPSF measurement by scintigraphy, 89 had HPSF > 10%, and 80 of these patients received RE treatment (Fig 1). Chemoembolization alone was performed in two patients, and no liver-directed treatment was performed in seven because of clinical deterioration (n = 6) or variceal hemorrhage (n = 1). One patient had HPSF of 23% with expected lung dose of 151 Gy, but preemptive transarterial chemoembolization performed twice, once with doxorubicin-eluting 100–300 μm LC Beads (BTG International, Farnham, United Kingdom), once with doxorubicin-eluting 50–100 μm QuadraSpheres (Merit Medical Systems), increased HPSF to 30%, so RE was not performed (Table 2).

Risk Factors
The mean and median HPSF in all 409 patients were 8.3% (SD ± 6.9%) and 6.4% (range, 0.5%–54%), respectively. HPSF > 10% was demonstrated in 32% (n = 43 of 134) of patients with HCC and 17% (n = 46 of 275) of patients with other cell types (Fig 3). Multiple linear regression analysis performed to evaluate risk factors for elevated HPSF demonstrated that HCC, HVTT, and PVTT correlated with increased HPSF (correlation coefficients 0.20, 0.27, 0.30; all P < .001). Previous transarterial chemoembolization and previous ablation were not correlated with HPSF (P = .27 and P = .47). When stepwise multiple regression analysis was performed to control for covariables, only HVTT and PVTT (and not HCC) demonstrated significant impacts on HPSF (both P < .001), with this model explaining 14% of the variability in HPSF (P < .001). The β coefficients associated with HVTT and PVTT were 10.5% and 5.9%, so that a patient with HVTT and PVTT would have 16.4% absolute higher HPSF than a patient without tumor thrombus in this model.

Of patients with HPSF > 10%, 89% (n = 80 of 89) received RE treatment. Excluding patients who were not treated because of clinical deterioration, dose reduction and adjunctive catheter techniques allowed for the treatment of 97.5% (n = 80 of 82) of patients with HPSF > 10%. Of the treated patients, the median HPSF was 14.1% (range, 10%–54%); 54 (68%) were male, and 36 (45%) were treated for HCC. The efficiency percentage

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>HVTT</th>
<th>PVTT</th>
<th>HCC</th>
<th>Initial HPSF (%)</th>
<th>Intervention</th>
<th>Post HPSF (%)</th>
<th>Absolute HPSF Reduction (%)</th>
<th>Relative HPSF Reduction (%)</th>
<th>Intervention during RE</th>
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<tr>
<td>HCC</td>
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<td>No</td>
<td>44</td>
<td>21</td>
<td>Retropitoneal VCE and BAE (600–700 μm SE)</td>
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<td>51</td>
<td>HVBO</td>
<td>29</td>
</tr>
<tr>
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<td>No</td>
<td>Yes</td>
<td>25</td>
<td>26</td>
<td>BAE (1,005–1,400 μm PVA)</td>
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<td>3</td>
<td>23</td>
<td>HVBO</td>
<td>29</td>
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<tr>
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<td>24</td>
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<td>23</td>
<td>46</td>
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<td>24</td>
<td>BAE (300–500 μm SE)</td>
<td>17</td>
<td>37</td>
<td>69</td>
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</tr>
<tr>
<td>HCC</td>
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<td>No</td>
<td>54</td>
<td>24</td>
<td>Transarterial chemoembolization</td>
<td>17</td>
<td>37</td>
<td>69</td>
<td>No RE performed</td>
<td>30</td>
</tr>
</tbody>
</table>

Table 2. Change in HPSF of Seven Patients Who Underwent Repeat 99mTc-MAA Scintigraphy after Shunt Reduction Intervention

BAE = bland arterial embolization; HCC = hepatocellular carcinoma; HVTT = hepatic vein tumor thrombus; PVTT = portal vein tumor thrombus; RE = radioembolization; RP = radiation pneumonitis; SE = spherical embolics; 99mTc-MAA = technetium-99m-labeled macroaggregated albumin; VCE = variceal coil embolization.
of microsphere delivery after a single flush of the V-vial was 94.4% for glass microspheres and 89.3% for resin microspheres compared with 97.0% for three or more flushes in patients who underwent normal delivery.

**Repeated Scintigraphy**

In seven patients who underwent repeat scintigraphy after HPSF mitigation, a median absolute reduction of 16% (range, 7% increase to 37% decrease) and a relative reduction of 40% (range, 32% increase to 69% decrease) was achieved (Table 2). In the two patients whose HPSF was not reduced, one underwent bland arterial embolization with very large PVA particles (1,000–1,400 μm), and the other underwent two drug-eluting microsphere transarterial chemoembolization procedures. The other five patients all had an absolute reduction of at least 7.2% (range, 7.2%–37%) and relative reduction of at least 29% (range, 29%–69%) (Fig 4a, b). In these patients with successful mitigation, embolic particle size was 300–900 μm. The patients who underwent variceal embolization showed relative reductions of 51% (in conjunction with bland arterial embolization) and 29% and did not manifest signs or symptoms of worsened portal hypertension.

**Pulmonary Toxicity**

Follow-up CT scans of the lungs were available in 55 of 80 treated patients (median follow-up period, 154 d; range, 13–2,050 d). Clinical follow-up data were available in all patients (median follow-up, 137 d; range, 6–2,134 d). Within the first 4 months of follow-up, no patients developed respiratory complications suspicious for RP. Of the 17 patients treated with dose reductions only, 12 were treated with 20% reduction, and 5 were treated with 40% reduction. None of the patients showed evidence of pulmonary toxicity. Similarly, of the 38 patients who received no dose reduction or shunt mitigation because of low expected lung dose, none showed evidence of pulmonary toxicity.

Two patients (2.6%) with high HPSF treated with shunt mitigating techniques developed delayed respiratory complications and radiographic findings suspicious for RP. Both patients were asymptomatic after RE but developed delayed complications after subsequent transarterial chemoembolization. In the 80 patients with HPSF > 10%, 16 patients underwent 23 transarterial chemoembolization procedures after RE (median, 1; range, 1–6; conventional transarterial chemoembolization, n = 11; drug-eluting microsphere transarterial chemoembolization, n = 12). RP was not observed in any of the 64 patients who did not undergo transarterial chemoembolization after RE (12.5% vs 0%, P = .04).

The first patient was a 58-year-old woman with metastases from intracranial hemangiopericytoma (whole-liver volume = 3,192 mL, estimated tumor replacement = 50%) (Fig 5a). Using the body surface area method, whole-liver activity prescription was 2.28 GBq. HPSF was 27.7%, and estimated lung exposure without shunt mitigation was 32 Gy. Hepatic vein balloon occlusion and immediate bland arterial embolization using 4 vials of 300–500 μm Embospheres were performed. This asymptomatic patient underwent transarterial chemoembolization 3 months later to treat residual disease supplied by parasitized phrenic arteries, receiving 150 mg doxorubicin on 100–300 μm and 300–500 μm LC Beads. She developed dyspnea on exertion 1 month later, which was 4 months after RE. CT revealed coarse peribronchial consolidation and ground-glass opacity, suggestive of RP (Fig 5b, c). Pulmonary function tests showed restrictive physiology with forced vital capacity 54% of predicted and diffusion capacity of the lung for carbon monoxide 62% of predicted. She resumed recreational physical activities on corticosteroid therapy (prednisone 40 mg/d tapering to 12.5 mg/d), and pulmonary function tests improved to forced vital capacity of 66% and diffusion capacity of the lung for carbon monoxide of 80%. She tolerated four additional transarterial chemoembolization treatments and remains on active surveillance 46 months after RE treatment, with scarring and mild bronchiectasis on follow-up imaging.

The second patient was a 72-year-old woman with focal HCC in segment 7 and infiltrative HCC with left hepatic vein and inferior vena cava tumor thrombus in segments 2 and 3. The HPSF was 22.6%. Using 200-Gy
target segmentectomy dose, the prescription was 3.48 GBq total (2.26 GBq to segments 2 and 3 and 1.28 GBq to segment 7), and estimated lung exposure without shunt mitigation was 39 Gy. Only segments 2 and 3 with tumor thrombus were treated with prophylactic techniques. Dose administration was followed by immediate N-butyl cyanoacrylate glue embolization via a parallel microcatheter. Follow-up showed a 92% decline in serum α-fetoprotein (221 ng/mL to 18 ng/mL), complete response in segment 7, and nearly complete response in segments 2 and 3 by modified Response Evaluation Criteria in Solid Tumors criteria (12). A chronic cough caused by Mycobacterium avium complex was stable, and the lungs were clear on CT. The patient underwent transarterial chemoembolization 4 months later to treat residual segment 4 disease, receiving 75 mg doxorubicin on 100–300 μm LC Beads. The patient developed dyspnea and tachypnea 2 months later, 6 months after RE, requiring home supplemental oxygen. CT showed metastatic nodules and peribronchial consolidation not

Figure 4. (a) Anterior view of planar scintigraphy after administration of $^{99m}$Tc-MAA into the proper hepatic artery in a 60-year-old man with HCC and PVTT showed pronounced uptake in the lungs, reflecting a high HPSF of 43.7%. (b) The patient underwent coil embolization of the right adrenal vein, which was the systemic outflow from arterioportal and portosystemic shunting, and bland arterial embolization of the right hepatic artery using 700–900 μm spherical embolic agents 14 days later. The HPSF was reduced to 21.4%, and focal uptake was evident in the intrahepatic tumors.

Figure 5. (a) Right anterior oblique surface rendering of a contrast-enhanced cone-beam C-arm CT scan of a 58-year-old woman with metastatic hemangiopericytoma before RE demonstrated large, hypervascular tumors with early opacification of the right and left hepatic veins (arrows). Dilute contrast material (150 mg iodine/mL) was injected into the common hepatic artery at 2 mL/s for 12 seconds, and imaging was performed in the last 8 seconds after a 4-second delay. $^{99m}$Tc-MAA scintigraphy yielded HPSF of 27.7%, which combined with an activity prescription of 2.28 GBq and estimated lung mass of 1 kg would have resulted in a pulmonary absorbed dose of 32 Gy. This patient underwent whole-liver RE with temporary occlusion balloons in the right and left hepatic veins and bland arterial embolization using 4 vials of 300–500 μm spherical embolic agents immediately after RE administration. (b) Coronal reconstruction of thoracic CT image obtained 10 weeks after RE showed no abnormalities in the asymptomatic patient. (c) Coronal reconstruction of thoracic CT image obtained 4 weeks after transarterial chemoembolization and 4 months after RE demonstrated bilateral coarse peribronchial consolidation and ground-glass opacity that spared the periphery. This imaging pattern, combined with pulmonary function tests indicating a restrictive pattern with decreased diffusion, was diagnostic of RP, possibly triggered by a radiation recall mechanism after exposure to doxorubicin.
typical of *Mycobacterium*. She declined further treatment and died in hospice.

**Imaging Response and Dose Reduction**

Response evaluation at 3-month follow-up evaluation was possible in 31 of 41 patients treated with resin microspheres; 16 (including eight treated with adjunctive techniques) were treated without dose reduction, and 15 (including five treated with adjunctive techniques) were treated with dose reduction. Objective radiographic response was observed in 13% of patients (n = 2 of 15) treated with dose reduction compared with 56% (n = 9 of 16) treated without dose reduction (P = .023). Disease control rate was 47% (n = 7 of 15) in patients treated with dose reduction compared with 94% (n = 15 of 16) without dose reduction (P = .006) (Table 3).

### Table 3. Objective Response and Disease Control Rates after RE for Patients Treated with Resin Microspheres

<table>
<thead>
<tr>
<th>Dose Reduction</th>
<th>No Dose Reduction</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (n = 15)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>SD</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Objective response (CR + PR)</td>
<td>13%</td>
<td>56%</td>
</tr>
<tr>
<td>Disease control (CR + PR + SD)</td>
<td>47%</td>
<td>94%</td>
</tr>
</tbody>
</table>

CR = complete response; PR = partial response; RE = radioembolization; SD = stable disease.

before the treatment decreased the measured HPSF by 65%–78% but inexplicably did not protect against pneumonitis. Consensus guidelines subsequently were developed for the use of resin microspheres recommending decreasing the administered activity by 20% in patients with 10%–15% HPSF, decreasing the administered activity by 40% in patients with 15%–20% HPSF, and avoiding RE treatment in patients with HPSF > 20% (SIR-Spheres yttrium-90 microspheres [package insert] Lane Cove, Australia: Sirtex Medical, Ltd, 2004.). Guidelines also recommend restricting radiation-absorbed dose to the lungs to < 30 Gy in a single exposure or 50 Gy over a lifetime (14).

These recommendations are not universally accepted. In a series of 58 patients with a cumulative lung dose > 30 Gy, no patients were found to have radiographic or clinical evidence of RP (15). This cohort included 19 patients with cumulative lung dose > 50 Gy. Guidelines for whole-liver treatment are not valid for treatment of smaller territories; treatment of a fraction of the liver results in a smaller total number of microspheres shunted if shunting is uniform throughout the liver. A large percentage of a small dose often does not exceed the 30-Gy threshold. Conversely, focal shunting may be underestimated and averaged by whole-liver 99mTc-MAA scintigraphy. Because response correlates in part to tumor absorbed dose (16), decreasing administered activity could lead to subtherapeutic dosing and poor response. Although still subject to error, calculation of absorbed dose to the lungs should be a more logical basis for adjustment of administered activity than the current oversimplified guidelines.

Even when administered correctly with the microcatheter positioned at the planned location of RE, 99mTc-MAA distribution may not exactly model 90Y activity distribution (17). 99mTc-MAA particle sizes are heterogeneous, and approximately 10% are < 10 μm in diameter, resulting in an overestimation of HPSF (18). Scatter from high 99mTc-MAA concentration in the liver may also artifactually increase calculated deposition in the right lung base (19). Streaming and clumping are other possible sources of mismatch between 99mTc-MAA and 90Y microsphere distribution. Other techniques of calculating HPSF, such as dynamic contrast enhancement studies of hepatic vein opacification (20) or using imageable 30-μm microspheres (18), may improve accuracy in the future.

High HPSF occurs more frequently in patients with HCC but is uncommon with other cell types, leading some investigators to suggest foregoing scintigraphy in patients with cell types other than HCC (21). Our cohort demonstrated that a substantial number of metastatic tumors also result in high HPSF. After controlling for macrovascular invasion, HCC was not significantly associated with increased HPSF.

Previously reported techniques to reduce hepatopulmonary shunting include systemic sorafenib (22) or transarterial
chemoembolization (23,24). Sorafenib treatment duration ranged from 72 to 297 days before repeat 99mTc-MAA imaging and subsequent 90Y treatment and was able to reduce HPSF by 62%-87%. Transarterial chemoembolization in patients with infiltrative HCC with portal venous invasion resulted in reduction of HPSF by 25%-57%. Although sorafenib and transarterial chemoembolization may also have antitumoral efficacy, their use to reduce shunting may delay RE treatment, and many candidates for RE are patients who have already failed these treatments.

Shunt mitigation techniques that may be employed on the day of treatment include temporary balloon occlusion of hepatic veins, which can reduce HPSF by an estimated 80%-90% (9). Similarly, embolization of varices in patients with arteriportal and portosystemic shunting blocks routes carrying shunted material to the lungs. A similar technique of temporary portal vein balloon occlusion has been used for transarterial chemoembolization in patients with arteriportal shunting (25).

Bland arterial embolization long before RE was shown to be ineffective and resulted in several cases of fatal RP, likely from recurrence of shunting (26). Bland arterial embolization is probably more effective performed on the day of treatment (26), but its effectiveness in reducing shunting is difficult to measure and to optimize. Too much bland arterial embolization before RE could redirect the 90Y microspheres to nontarget background liver or cause premature stasis and insufficient dose. Too little or too late bland arterial embolization could allow 90Y microspheres to traverse shunts before achieving stasis. Repeat scintigraphy after bland particle embolization in a few patients established a range of expected effect of up to 50% reduction, with better shunt reduction using midsized particles. To avoid washout of microspheres before stasis is achieved, we found that use of two parallel microcatheters and glass microspheres to achieve a tight bolus allowed us to achieve almost instantaneous stasis after delivery of 90Y microspheres.

Both of our patients who developed delayed RP presented with signs or symptoms only after subsequent transarterial chemoembolization. It is unknown whether their pulmonary toxicity was simply delayed in onset or was triggered by transarterial chemoembolization. RP secondary to external-beam radiotherapy typically manifests within 8 weeks after exposure (13), and previous accounts of RE-related RP reported onsets 1–4 months after RE treatment (4,5). Circulating chemotherapeutic agent after transarterial chemoembolization possibly played a role in our patients. “Radiation recall” is a well-described phenomenon where systemic chemotherapy, especially taxanes and anthracyclines such as doxorubicin, given after radiation can reactivate and accentuate the effect of radiation on the skin or lungs (27). Although the exact mechanism of action is unclear, interference with repair of irradiated lung parenchyma, changes in microvascular permeability, and damage of stem cells have been proposed. Some data suggest that sequential radiotherapy and chemotherapy may be more toxic to the lungs than concomitant therapy (28). However, corticosteroid therapy is typically effective and may allow additional chemotherapy treatment, as with one of our patients.

Patients treated with resin microspheres according to dose reduction guidelines had worse outcomes, with lower objective response and disease control rates. These results corroborate prior reports that found response and survival to correlate with hepatic and tumor absorbed doses (16,29). It is unknown if the use of adjunctive techniques, particularly bland arterial embolization, contributed to better response rates in patients treated without dose reduction. Patients with high HPSF are at particular risk for subtherapeutic dosing because high HPSF and dose reduction reduce the actual absorbed tumor dose. For example, if a patient with a 20% HPSF is treated with the recommended 40% dose reduction, the absorbed dose to the liver is only 48% of the originally intended dose: (100% – dose reduction) × (100% – HPSF). Ideally, real-time monitoring of tumor and liver dose would help define RE endpoints, and intraprocedural positron emission tomography may provide such feedback (30).

Limitations of this study include its retrospective nature and multiple treatment groups with small sample sizes and changing treatment algorithms over time. The variety of pathologic diagnoses (14 different cell types) and the various adjunctive techniques employed precluded a more detailed subgroup analysis because of limited sample sizes. Estimated lung absorbed doses based on MIRD calculations used only estimated lung mass, which was not accurately measurable. Only clinical toxicity was analyzed because actual pulmonary deposition of 90Y was not measurable. Diagnosis of RP lacked certainty because chronology was atypical and findings could have overlapped with other neoplastic, infectious, or toxic conditions including transarterial chemoembolization toxicity (31,32). Despite the suspicion for radiation recall, the actual etiology of toxicity is uncertain.

In conclusion, current recommendations for dose activity reduction for high HPSF are oversimplified, may compromise therapeutic efficacy, and are most often avoided without substantially increased risk of radiation pneumonitis. Instead of reducing the treatment dose, catheter-based techniques can be used to decrease the transit of microspheres into the lungs. Rather than using only the shunt fraction percentage, MIRD calculation of anticipated dose to the lungs, especially when total administered activity is low, should be a better metric for risk assessment. None of our patients with expected lung dose < 30 Gy experienced complications, including patients who underwent no prophylactic measures. For patients with higher anticipated lung dose, catheter-based techniques during RE treatment may successfully mitigate shunting.
REFERENCES


17. Ward et al


