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 ($\geq$ 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 $\geq$ 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 $\leq$ 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, ^{99m}Tc-MAA = technetium 99m–labeled macroaggregated albumin, ^{90}Y = yttrium-90

Complications and toxicities after yttrium-90 (^{90}Y) 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

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in luminal diameter, traverse the heart, and lodge in pulmonary arterioles. In addition, in patients with portal hypertension and varices, microspheres can pass through arterioportal 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 distribution. Early studies on whole-liver RE treatment associated the risk of RP with the hepatopulmonary shunt fraction (HPSF) (5) and led to consensus guidelines dictating that 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 ± 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 $<$ 30 Gy and the cumulative lung dose was $<$ 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

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

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)