ELSEVIER

Techniques in Vascular and Interventional Radiology

Management of High Hepatopulmonary Shunts in the Setting of Y90 Radioembolization

Brian J. Schiro, MD, Edgar St. Amour, MD, Christopher Harnain, MD, and Ripal T. Gandhi, MD

Treatment paradigms for primary and metastatic malignancies involving the liver have evolved in recent years to include targeted liver therapies. Transarterial radioembolization is at the forefront of therapy in many treatment algorithms. However, due to significant hepatopulmonary shunting, some patients are excluded from this proven treatment due to the possibility of radiation-induced lung injury. In this article, we review techniques to mitigate hepatopulmonary shunts to improve the likelihood of inclusion and successful treatment in these patients.
Tech Vasc Interventional Rad 22:58-62

KEYWORDS radioembolization, hepatopulmonary shunt, radiation induced lung disease

Introduction

The modern evolution of cancer treatments has accelerated interventional oncology and placed it at the forefront of therapy. Ablative techniques have long been recognized as a first-line therapy for limited hepatic metastases and primary malignancies.[1] Transarterial chemoembolization (TACE) has direct indications for treatment of intermediate stage hepatocellular carcinoma, and compelling data exist for TACE and transarterial radioembolization (TARE) in the treatment of other stages of hepatocellular carcinoma (HCC) and colorectal cancer as well as other hepatic metastases.[2-4]

Most recently, TARE has been shown to be effective as a first-line therapy for even early stages of HCC.[5] Not all patients are candidates for this life-extending, or sometimes life-saving, treatment due to a number of technical and clinical factors. For instance, patients with hepaticoenteric communications (eg, supraduodenal arteries, right gastric artery, etc) that cannot be excluded from the arterial treatment site—via embolization or other methods—cannot safely undergo TARE due to the potential for gastrointestinal complications, namely radiation-induced gastroenteric ulcers. Furthermore, patients with high hepatopulmonary shunts (HPS; Fig. 1) often times are also excluded from TARE due to the potential for radiation-induced lung injury (RILI).

Miami Cardiac & Vascular Institute, Miami Cancer Institute, Miami, FL.
Address reprint requests to Brian J. Schiro, MD, Miami Cardiac & Vascular Institute, Miami Cancer Institute, 2nd Floor, 8900 N. Kendall Drive, Miami, FL 33131. E-mail: BrianSc@baptisthealth.net

The pathophysiology for HPS is related to vascular growth factors in the local tumor environment and subsequent neovascularity with formation of irregular vessels with large diameters allowing for passage of particles larger than 45 μm from the hepatic artery to hepatic veins. In the setting of TARE, this could allow for excessive shunting from the liver and into the central circulation and ultimately into the lungs. RILI may lead to pneumonitis or fibrosis. Pneumonitis typically occurs 1-3 months after radiation exposure with symptoms of a low-grade fever, nonproductive cough, and progressive exertional dyspnea. Chest imaging classically demonstrates patchy consolidation with sparing of the periphery and fissures (ie, bat-wing appearance), atelectasis, and pleural effusions. Fibrosis progresses over 6-24 months and can lead to debilitating pulmonary hypertension and cor pulmonale with a restrictive pattern of lung disease.[6] Steroids are the mainstay of treatment in the acute phase of the disease, with bronchodilators and supplement oxygen given for supportive therapy. Pentoxifylline may also be considered as it is radioprotective and prevents early and late pulmonary toxicity. In this article, we review the techniques for managing and mitigating high HPS and discuss methods for reducing shunt fractions.

Clinical Evaluation of the Patient

All oncology patients require a multidisciplinary evaluation with a team of cancer specialists. Tailored therapies for individual patients should be decided at local tumor boards and

 1089-2516/14/$-see front matter
https://doi.org/10.1053/j.tvir.2019.02.004

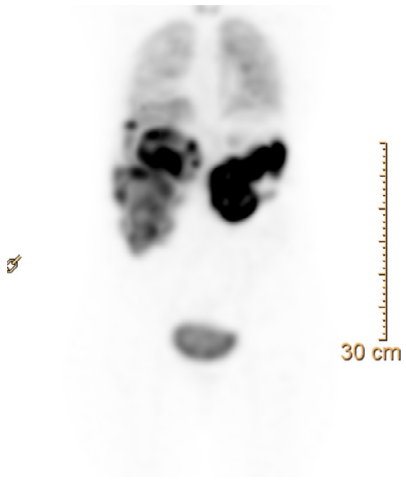

Figure 1 SPECT imaging following Tc-MAA mapping procedure in a patient with multifocal HCC demonstrates significant uptake in the lungs with a lung shunt of > 20%.

based on data-driven, proven treatments with a board consensus for each patient. As such, it is imperative that interventional oncologists are present and provide valuable input into the multidisciplinary decision for treatment.

Once targeted liver therapy with TARE has been selected for a patient, independent clinical evaluation should be completed by the interventionalist with a dedicated office consultation, as with all interventional oncology patients. At that time, a complete history and physical exam should be performed with notation made of the cancer tumor type including histology and biomarkers, stage of disease, previous and current cancer treatments, eastern cooperative oncology group (ECOG) performance status, and life expectancy. A frank discussion on the goals of treatment (eg, palliative vs curative vs bridge to transplant) should be had along with risks and expected outcomes of the procedure.

The patient should be notified at the initial consultation that not all patients are candidates for the procedure, and that high HPS may limit efficacy or result in unacceptable risk. If TARE is elected, the patient must undergo a pretreatment angiogram with technechium-99m macroaggregated albumin (Tc-99m MAA) mapping to determine patient candidacy for TARE (eg, assess the extent of the HPS and unidentified gastroenteric communications).

Indications for the Procedure

Traditionally, HPS is considered significant if the lung shunt fraction is >10%-20% with recommended dose reductions of 20%-40%. However, in our opinion, these percentages are arbitrary and oversimplified. Furthermore, the resin radiomicrospheres (Sir-Spheres) Instructions for Use has recently changed and is now similar to the glass radiomicrospheres (Theraspheres) Instructions for Use in terms of maximum dose allowable to the lungs. More accurately, a significant HPS is one in which the patient receives a total lung dose of 30 Gy in a single TARE treatment session or 50 Gy in a lifetime.[7] The overall percentage of the shunt is not as important as the absolute dose delivered to the lungs. From a safety

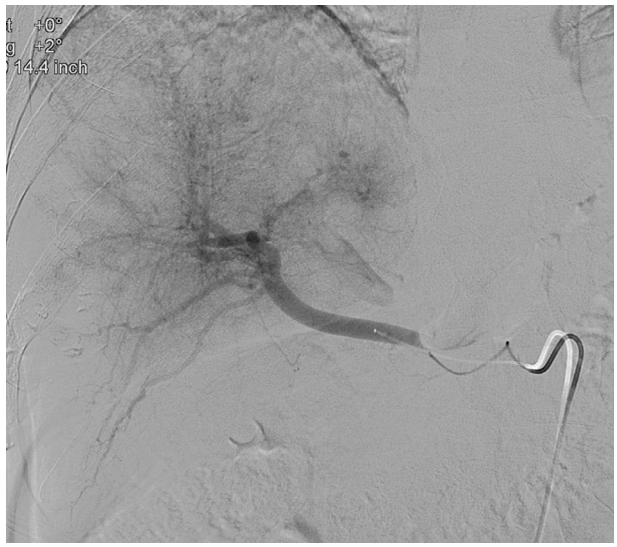

Figure 2 Evidence of hepatic artery to portal vein shunting in a patient with HCC and tumor thrombus in the portal vein. Vascular invasion is a risk factor for increased lung shunt.

standpoint, it is advisable to be more conservative in patients with baseline pulmonary compromise due to chronic obstructive pulmonary disease, previous lung surgery, or other factors.

HPS is most common in hypervascular tumors, including HCC and certain metastases. Risk factors for HPS include hepatocellular carcinoma and portal vein or hepatic vein tumor thrombus.[8] Patients with CT or angiographic evidence of shunting to the portal veins (Fig. 2) or hepatic veins are at increased risk for having a significant HPS. Furthermore, patients with HCC with or without portal vein invasion have a 20%-32% chance of significant HPS.[8,9] Additional risk factors include large tumor burden and infiltrative disease.

Equipment Needed

The necessary equipment will depend on the method of shunt management (Table). This will be detailed in the following sections. Many methods are catheter based and require standard angiographic equipment with procedures performed under moderate sedation in most instances.

Procedural Steps

Bland/Chemoembolization to Reduce Lung Shunt

Standard techniques of bland embolization or chemoembolization can be employed to decrease lung shunt fraction.[8] Large particles should be used during embolization to shut down large arteriovenous and arterioportal shunts. We typically use Embospheres 500-700 μm in size. A technical pearl is to avoid the typical slow flow or stasis endpoint for the bland embolization or chemoembolization procedure as this may preclude subsequent TARE. The goal is to decrease the shunt without occluding the target vessels. Gaba and Lakhoo

Table Lists Various Methods to Reduce HPS

Methods to Reduce Lung Shunt	Treatment Summary
Bland/chemoembolization	Use large particles (eg, Embospheres 500-700 μm) to treat the shunt and follow-up with RE in 10-14 d.
Low-dose TARE	Calculate dose to deliver <30 Gy during the first treatment, repeat mapping to reassess lung shunt fraction and deliver additional dose not to exceed a lifetime of 50 Gy to the lungs.
Segmental TARE	Perform segmental RE with dose <30 Gy, perform subsequent segments 4-6 wk later and deliver additional dose not to exceed a lifetime of 50 Gy to the lung.
Hepatic vein occlusion balloons	Perform hepatic vein balloon occlusion with compliant balloons (eg, 5.5 French Fogarty) in the middle and treatment side veins prior to delivery. Remove balloons 1-5 min postdelivery.
Collateral portosystemic outflow embolization	Embolization of competing outflow veins in cirrhotic livers with hepatofugal flow.
Chemotherapy	8-12 wk following systemic treatment, repeat mapping to reassess lung shunt fraction.

reported 2 cases of HCC referred for radioembolization who had elevated lung shunt fractions.[10] One patient had portal vein invasion. Both patients were treated with chemoembolization (conventional TACE and drug-eluding beads each) with adequate reduction in the HPS. This allowed for successful TARE 10-14 days later without the development of RILI. In a similar report, Rose and Hoh described 2 patients with metastatic melanoma successfully treated with TARE following chemoembolization to treat an elevated lung-shunt fraction.[11] Ward et al showed a relative reduction of 29%-69% in HPS in 5 patients who had embolization procedures.[8]

Low-Dose Radioembolization to Reduce Lung Shunt

As an alternative to performing bland embolization or chemoembolization, attempts at offering a low-dose TARE have been reported. In this technique, TARE must be given in doses calculated to deliver less than 30 Gy during the first treatment session. After the procedure is performed, a second mapping study is done to reassess the lung shunt fraction. The lung shunt must be sufficiently low for the second treatment such that the dose delivered to the lungs is less than the maximum lifetime dose of 50 Gy to avoid toxicity.

A variation to this approach is to perform segmental TARE rather than lobar. Full dose TARE may be provided to a segment of involved liver such that the dose is less than 30 Gy. If full dose treatment of additional segments is required, this can be offered 4-6 weeks later, again with a dose not to exceed the maximum lifetime lung dose of 50 Gy. Repeat MAA mapping may be considered to the target segment with localized delivery of MAA to the region of interest. This will provide a more accurate assessment of HPS related to the segment.

Hepatic Vein Occlusion Balloons to Reduce Lung Shunt

In this technique, the pre-TARE mapping angiogram is performed with arterial access from standard techniques.[8,12] However, jugular venous access is also obtained to place 1 or more compliant balloons in the hepatic veins to temporarily decrease the venous outflow from the liver (Figs. 3 and 4).

In our practice, right jugular venous access is obtained with two 6F sheaths. This allows for passage of two 5.5F Fogarty balloons into the middle hepatic vein and the right or left hepatic vein (depending on the location of treatment). Prior to administration of Tc-99m MAA, the balloons are inflated. The agent is infused through the arterial access, and the balloons are deflated and removed 1-5 minutes later.

Bester and Salem reported this technique with 1 case of a patient with metastatic malignant insulinoma and 2 patients with metastatic colorectal cancer.[12] Initial Tc-99m MAA single photon emission computed tomograpy (SPECT) scan showed significant HPS precluding standard TARE. At the time of TARE with Y90 resin radiomicrospheres, occlusion balloons were inflated in the hepatic veins prior to administration and continued for 60 seconds following infusion. Tc-99m MAA was not repeated prior to treatment, and a

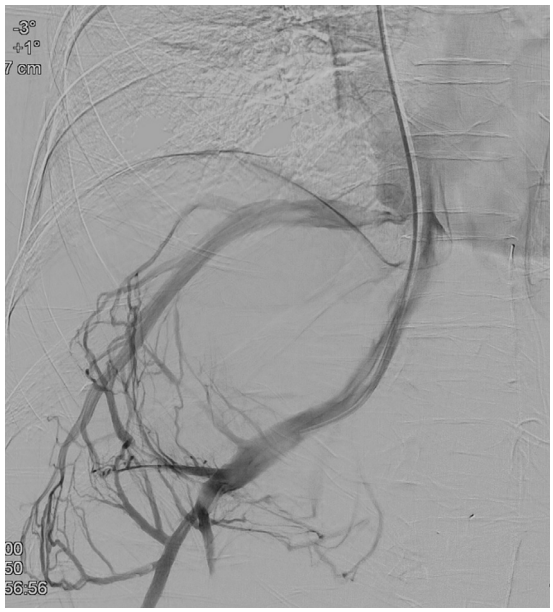

Figure 3 Venogram from a right internal jugular vein approach demonstrates the right and middle hepatic veins.

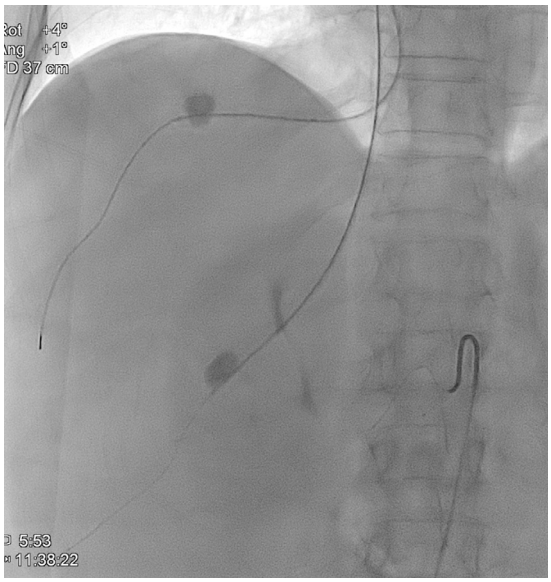

Figure 4 Balloon occlusion technique in which Fogarty balloons were placed and inflated in the right and middle hepatic veins in order to decrease hepatopulmonary shunting.

40% activity reduction was prescribed in order to account for the possible HSP. A follow-up Bremsstrahlung SPECT showed significant reduction in the HPS. However, it is difficult to generalize this to other patients as the Bremsstrahlung scan is less sensitive and specific for assessing the HPS. One may consider aspirating on the occlusion balloons prior to deflation on the day of the TARE procedure in case there are any radiomicrospheres in the hepatic vein. The occlusion balloons and the aspirated material should be disposed of in the Nalgene waste container as they may contain radioactive spheres.

Embolization of Collateral Portosystemic Outflow

In patients with cirrhosis and advanced liver disease, portal hypertension may develop. Hepatoportal arteriovenous shunts may develop with recruitment of collateral portosystemic outflow veins, for example, recanalized paraumbilical veins and gastroesophageal varices. With hepatofugal flow in the portal veins, substantial shunting through collateral veins may result in high HPS. Percutaneous embolization of these veins has been reported in an attempt at reducing HPS prior to TARE.[8]

Chemotherapeutic Treatment to Reduce Lung Shunt

In patients with HCC and elevated lung shunts, pretreatment with the multiple tyrosine kinase inhibitor sorafenib has proven effective at reducing the HPS. Theysohn et al reported on 7 patients with elevated HPS who underwent treatment with sorafenib for a mean of 138 days (range 72-297 days).[13] Liver mass protocol CT scans of the abdomen were used to assess when tumors were adequately reduced for repeat Tc-99m MAA evaluation. Three of the patients had progression of disease over time and did not survive to undergo TARE. The remaining 4 patients had significant reduction in their HPS and had successful TARE treatment.

Similarly, for patients with metastatic disease, pretreatment with targeted chemotherapy has been used to improve the lung shunt fraction. In a retrospective analysis of 62 patients with liver metastases from colorectal cancer, Deipolyi et al showed a low HPS following TARE in patients who received chemotherapy prior to treatment.[14] Surprisingly, these patients also had the longest survival in those with HPS. The authors postulate that "normalizing" the tumor vascularity with chemotherapy reduces the abnormal vessels, including shunts, and reduces angiogenesis, thus increasing blood flow to the tumors making them more responsive to TARE.

Overcoming Technical Challenges

Although the above techniques have shown independent efficacy in reducing HPS, a combination of these procedures is often required to sufficiently overcome this obstacle. In HCC, for instance, performing chemoembolization and treating with sorafenib has been necessary in patients with high HPS. Ward et al reported using balloon occlusion techniques and bland/chemoembolization to successfully reduce HPS.[8]

In patients with high HPS who are to be treated with chemotherapy to reduce the HPS, the main challenge is balancing the time between treatment and performing TARE. Sufficient time must be given for efficacy of the chemotherapeutic regimen to reduce the HPS. In patients with fast-growing tumor types, the window of opportunity to treat with TARE may be lost. In general, repeat MAA mapping should be performed 8-12 weeks after chemotherapy is initiated. If vascular endothelial growth factor inhibitors are used (eg, bevacizumab), these medications should be held for at least 4 weeks prior to arterial catheterization as they may lead to friability of the vasculature with resultant vascular irregularity, spasm, and dissection with manipulation.

Recognizing and Treating Complications

Complications of the various procedures to reduce hepatopulmonary shunts are centered around the respective mitigation options. For instance, postembolization syndrome associated with bland embolization and chemoembolization are the most common repercussions of this treatment. If smaller particles are used, attention should be given when excessive amounts of embolic material are required. This may reflect large arteriovenous shunting and could result in significant pulmonary embolization leading to pulmonary injury, respiratory compromise, fibrosis, and even death. The theoretical risk of right-to-left heart shunts should not be overlooked in patients with cirrhosis. High venous pressures may increase blood flow through a patent foramen

ovale or atrial septal defects. Stroke risk is a theoretical concern; however, we do not routinely perform studies to evaluate for shunting.

With the use of chemotherapy to reduce HPS, side effects vary with the potential treatment regimens. If patients cannot tolerate the effects, selecting a different method to reduce the HPS should be offered promptly to preclude further shunt progression.

Clinical Follow-Up

Clinical follow-up is necessary and routine following any IO procedure performed to assess treatment and postprocedure complications. We routinely evaluate patients within 2 weeks of treatment with TACE or TARE for general health and early complication assessment.

After performing one of the mitigation options, it is our practice to repeat Tc-99m MAA mapping to ensure that the HPS has been meaningfully reduced. This should be done within 2 weeks of bland- or chemoembolization to prevent new collateral pathways from developing and 4 weeks after radioembolization to allow treatment efficacy and tumoral reduction. Provided that there is adequate reduction of the HPS, it is critical to schedule TARE within a week of the mapping study to prevent interval development of new and additional shunting. If treating with chemotherapy for reduction of HPS, follow-up mapping in 8-12 weeks is suggested as discussed above.

Expected Outcomes

With no randomized data and little retrospective data available, early and late outcomes of these techniques are not well established. In a retrospective analysis of 89 patients, Ward et al estimated that 89% of patients with high HPS were able to successfully undergo TARE following the above options. No patients developed radiation pneumonitis at 4 months, but 2 patients had signs suggestive of pulmonary fibrosis after chemoembolization procedures performed at later intervals. More data are necessary to fully advise patients on efficacy and prevention of RILI.

Of note, when performing activity reduction in the setting of a high HPS to decrease the lung dose <30 Gy during a single administration (or <50 Gy lifetime), it is important to ensure that the tumor is still getting adequate dose to be tumoricidal. Although conventional teaching is the need for reducing the administered Y90 activity in the setting of high HPS, for some patients it is necessary to actually increase the activity to achieve a tumoricidal dose as long as the dose to the lungs is below the thresholds described.

Conclusion

In conclusion, several methods are available to manage high HPS in patients undergoing TARE and complications can be prevented with appropriate patient selection, careful treatment planning, meticulous use of the techniques described in this article, and optimization of dose. The best treatment method has not been elucidated, and multiple techniques may be necessary to successfully mitigate the HPS.

References

1. Padia SA, Lewandowski RJ, Johnson GE, et al: Radioembolization of hepatic malignancies: Background, quality improvement guidelines, and future directions. J Vasc Interv Radiol 28:1-15, 2017
2. Lewandowski RJ, Kulik LM, Riaz A, et al: A comparative analysis of transarterial downstaging for hepatocellular carcinoma: Chemoembolization versus radioembolization. Am J Transplant 9:1920-1928, 2009
3. Ruers T, Van Coevorden F, Punt CJ, et al: Local treatment of unresectable colorectal liver metastases: Results of a randomized phase II trial. J Natl Cancer Inst 109:1-10, 2017
4. Llovet JM, Bru C, Bruix J: Prognosis of hepatocellular carcinoma: The BCLC staging classification. Semin Liver Dis 19:329-338, 1999
5. Salem R, Gabr A, Riaz A, et al: Institutional decision to adopt Y90 as primary treatment for hepatocellular carcinoma informed by a 1,000-patient 15-year experience. Hepatology 68(4):1429-1440, 2018
6. Graves PR, Siddiqui F, Anscher MS, et al: Radiation pulmonary toxicity: From mechanisms to management. Semin Radiat Oncol 20:201-207, 2010
7. Ho S, Lau WY, Leung WT: Ultrasound guided internal radiotherapy using yttrium-90 glass microspheres for liver malignancies. J Nucl Med 38:1169-1170, 1997
8. Ward TJ, Tamrazi A, Lam MG, et al: Management of high hepatopulmonary shunting in patients undergoing hepatic radioembolization. J Vasc Interv Radiol 26:1751-1760, 2015
9. Furuse J, Iwasaki M, Yoshino M, et al: Hepatocellular carcinoma with portal vein tumor thrombus: Embolization of arterioportal shunts. Radiology 204:787-790, 1997
10. Gaba RC, Lakhoo J: Yttrium-90 microsphere radioembolization for treatment of lung cancer hepatic metastases. Case Rep Oncol 5:479-486, 2012
11. Rose SC, Hoh CK: Hepatopulmonary shunt reduction using chemoembolization to permit yttrium-90 radioembolization. J Vasc Interv Radiol 20:849-851, 2009
12. Bester L, Salem R: Reduction of arteriohepatovenous shunting by temporary balloon occlusion in patients undergoing radioembolization. J Vasc Interv Radiol 18:1310-1314, 2007
13. Theysohn JM, Schlaak JF, Muller S, et al: Selective internal radiation therapy of hepatocellular carcinoma: potential hepatopulmonary shunt reduction after sorafenib administration. J Vasc Interv Radiol 23:949-952, 2012
14. Deipolyi AR, Iafrate AJ, Zhu AX, et al: High lung shunt fraction in colorectal liver tumors is associated with distant metastasis and decreased survival. J Vasc Interv Radiol 25:1604-1608, 2014