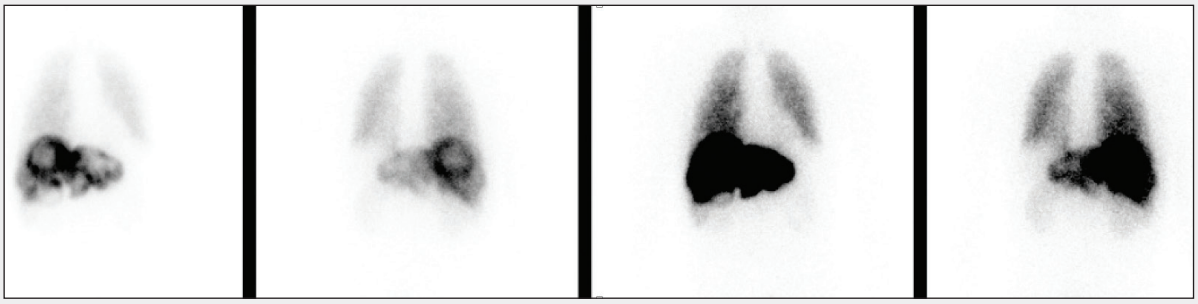
Liver Embolization

MODERATORS: DAVID M. LIU, MD, FRCPC, FSIR, AND RIPAL GANDHI, MD, FSVM
PANELISTS: ARAVIND AREPALLY, MD, FSIR; TOBIAS F. JAKOBS, MD; AND MARK WESTCOTT, MD

HIGH LUNG SHUNT (36%)



A Tc-99m microaggregated albumin (MAA) shunt scan after mesenteric artery optimization in preparation for yttrium-90 (Y-90) in a patient who had Child-Pugh class A with hepatocellular carcinoma (HCC) and portal vein invasion. The calculated lung shunt fraction revealed 37% shunting, resulting in > 30 Gy to the lungs.

What techniques may be employed to manage a significant lung shunt?

Prof. Jakobs: First, the angiographic images should be reevaluated for a potentially detectable arteriovenous fistula, which could be occluded/embolized. There is the potential to go more distal into the hepatic arterial system and therefore avoid or reduce the shunting into the lungs. This could imply that more than one treatment position might be necessary. Another option might be to coil embolize the segment, which most likely contributes to the shunt, and rely on intrahepatic redistribution for complete tumor coverage during treatment. Of course, a Tc-99m MAA study has to be repeated to confirm either a significant reduction or elimination of the shunt. If all these options fail, reduction of the activity has to be taken into account.

Dr. Westcott: I have had some success anecdotally with large-particle embolization (one was reduced from 50% to 25%). If there is a hepatic vein tumor, one can try external beam radiation therapy. Also, a month of sorafenib may reduce the lung shunt. Furthermore, Tc-99m MAA overestimates lung shunt due to a preponderance of MAA particles in the lower end of the 10- to 100-µm range.[1]

Dr. Arepally: An elevated lung shunt fraction (LSF) is defined as > 20%, which may result in nontarget pulmonary irradiation and radiation pneumonitis. Standard published guidelines recommend a lung dose no more than 30 Gy in a single transarterial radioembolization (TARE) procedure or no more than 50 Gy in multiple TARE sessions to the lung. In addition, guidelines suggest decreasing the administered activity by 20% in patients with a 10% to 15% hepatopulmonary shunt fraction (HPSF), decreasing the administered activity by 40% in patients with a 15% to 20% HPSF, and avoiding radioembolization in patients with a HPSF > 20%.

With an elevated LSF, four general techniques are typically described: (1) proceed with radioembolization, but confirm that the dosimetry to lung dose is below the recommended dose to minimize radiation pneumonitis; (2) in patients with a discrete vascular supply, perform simultaneous or separately bland embolization (or transarterial chemoembolization [TACE]) with large beads (> 300 µm) followed by repeat shunt studies; (3) initiate a short-term session with sorafenib with repeat planning at the end of the 3 months; and (4) temporary balloon occlusion of the hepatic veins or embolization of varices in patients with arterioportal and portosystemic shunting to the lungs.[2]

In the absence of large portosystemic varices, and given that this patient would receive a dose > 30 Gy to the lungs, I would initially perform a separate TACE session with large beads followed by a repeat MAA shunt study. If a repeat shunt study does not demonstrate adequate LSF reduction, then consider a short course of sorafenib followed by repeat planning study in 3 months.

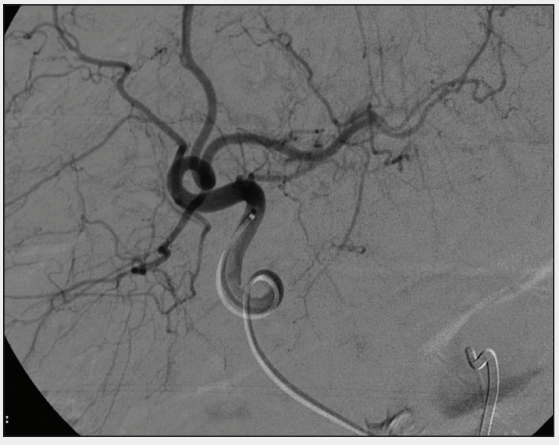
When does radiation pneumonitis occur, and how do you manage it?

Prof. Jakobs: Radiation pneumonitis is a rare complication that occurs after TARE, especially when the previously mentioned protective measures are followed. It usually occurs weeks to months after exposure. There is no consensus that a clinically significant radiation pneumonitis will occur, even in elevated LSFs. This might be due to the circumstances that the currently used Y-90 dosimetry models assume uniform distribution of the spheres/activity in the lungs, which is probably not the case. Treatment is aimed at decreasing the inflammatory process. Oral corticosteroids (eg, prednisone) are the mainstay of therapy for radiation pneumonitis, which are titrated over several weeks.

Dr. Westcott: This may occur after the lung receives > 25 Gy in a single session of TARE or a cumulative dose of 50 Gy. These dose limits should be decreased in patients with previous radiation, underlying lung disease, or previous resection. Symptoms occur several months after treatment. Treatment with oral and inhaled corticosteroids is recommended.

Dr. Arepally: Radiation pneumonitis is a rare phenomenon (< 1%), and we have rarely seen this in our clinical practice. In addition, radiation pneumonitis is very difficult to manage with no clear consensus on the optimal management strategies (ie, aggressive corticosteroid therapy vs conservative monitoring). Ideally, in high-risk patients (elevated LSF with history of pulmonary fibrosis), the potential for radiation pneumonitis should be extensively discussed with the patient at the clinic visit, along with a simultaneous consultation with pulmonary/critical care specialists.

METASTATIC COLORECTAL CANCER: HEPATIC ARTERIAL RESPONSE TO BIOLOGIC AGENTS ("AVASTIN EFFECT")



A 43-year-old woman with disseminated metastatic colorectal carcinoma of the liver was chemorefractory. Maintenance bevacizumab therapy (Avastin, Genentech, Inc.) was started. A mesenteric angiogram was obtained in preparation of resin-based Y-90 microsphere administration, which revealed significant attenuation of the hepatic arterial vasculature and sluggish antegrade flow.

What is your treatment algorithm for patients on bevacizumab therapy who require radioembolization?

Prof. Jakobs: There is no consensus on how to manage bevacizumab in a patient who is scheduled for TARE. Generally, most experts recommend pausing bevacizumab for at least 4 weeks before administering the TARE treatment.

Dr. Westcott: Stop bevacizumab therapy for 4 to 6 weeks prior to TARE and consider the use of capecitabine during this time period. Intra-arterial verapamil during TARE may improve flow.

Dr. Arepally: Patients who are on bevacizumab are at high risk for developing early stasis, severe vasospasm, and/or dissection, which can constrain the ability to target tumor vascularity. I typically wait at least 3 to 4 weeks from the last dose before I perform angiography.

What other chemotherapy or targeted agents can be problematic when performing hepatic angiography/Y-90 therapy? How long do you hold off on using these agents before and after radioembolization?

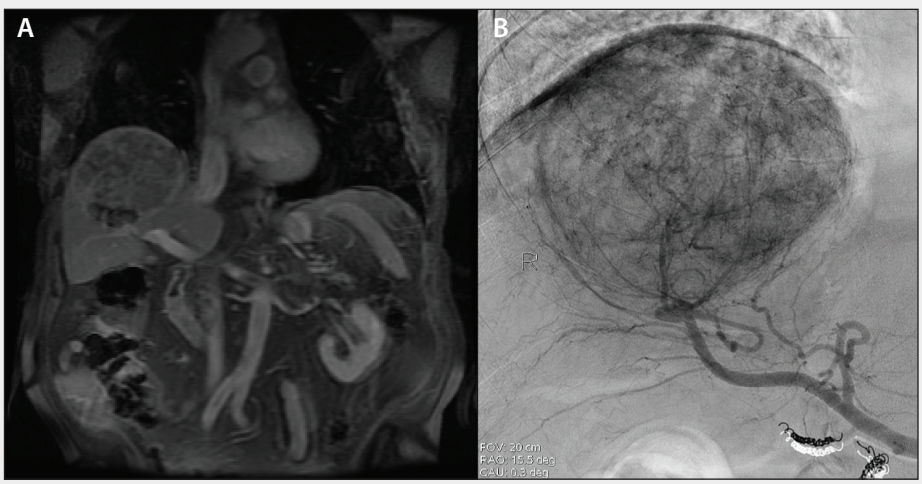
Prof. Jakobs: Initially, concurrent use of capecitabine with TARE was contraindicated due to concerns for significant liver toxicity. However, recent publications sug-

gest that capecitabine can be safely administered with Y-90 microspheres at doses typically utilized with combination chemotherapy.[3]

Dr. Westcott: Gemcitabine is also a significant radiosensitizer. I have had experience with a patient who underwent TARE and was started on gemcitabine soon after demonstrating a complete response at 2 months. The patient then developed radioembolization-induced liver disease at 3 months. Since then, I hold off on giving gemcitabine for at least 6 weeks. Neutropenia may occur in patients concurrently receiving oxaliplatin. Reduce the dose (from a standard 85 mg/m^2 to 60 mg/m^2) for 4 weeks after TARE, then resume the standard dose (as was done in the SIRFLOX and FOXFIRE/FOXFIRE Global studies).

Dr. Arepally: Pharmaceutical agents such as vascular endothelial growth factor inhibitors try to remodel or "normalize" the vascular flow to the tumor to enhance delivery of cytotoxic chemotherapeutic agents into the tumors. By reducing the vascular supply to the tumors, these agents reduce the tumoral interstitial pressure and enhance delivery of these systemic cytotoxic agents.[4,5] Although this improves systemic delivery of chemotherapeutic agents, this reduced vascularity restricts the ability to target tumors via an intra-arterial approach. Furthermore, this marked vascular reduction in tumor flow can be seen in all vascular endothelial growth factor inhibitors (eg, bevacizumab, regorafenib, sunitinib, sorafenib). Thus, with all of these agents, I typically wait 3 to 4 weeks after the last dose before performing angiography and attempt to restart the chemotherapy sessions usually within 1 to 2 weeks after the last Y-90 treatment. To minimize treatment delays, I typically perform planning studies and additional workup during the chemotherapy cycles. However, to avoid any associated toxicities related to chemotherapy, I typically wait 2 to 3 weeks after the last chemotherapy session before performing Y-90 treatment.

SOLITARY LESION (8 CM)



An 8-cm subcapsular HCC was seen on MRI (A) and angiography (B). Imaging further revealed a single vascular pedicle and extensive hypervascularity, with no evidence of necrosis.

In a patient who is not a surgical candidate, what is your approach to treating this lesion?

Prof. Jakobs: I would first consider performing TACE with drug-eluting beads for at least three sessions in a 4-week interval. If I do not see a response or if I detect disease progression, I would recommend TARE as the next option in the treatment algorithm.

Dr. Westcott: My approach would be selective TARE with a goal of achieving a tumor partition dose of 140 Gy to the tumor using the recently available DAVYR (Dosimetry and Activity Visualizer for Yttrium-90 Radioembolization) calculator* with selection of partition activity. More spheres result in greater tumor coverage; therefore, I prefer resin or EX Glass radiomicrospheres.

Dr. Arepally: Given the tumor size, location, and vascularity, I would prefer to use Y-90 in this setting. However, lesions that are typically subcapsular, such as this tumor, are notorious for recruiting additional

*Liu D. Available at the App store at https://itunes.apple.com/us/app/davyr-y90-radioembolization/id1038063189?mt=8.

extrahepatic supply. Therefore, prior to any treatment, I would perform CT angiography or detailed planning angiography utilizing cone-beam CT to assess for additional feeding arteries, such as the phrenic, intercostal, and/or phrenic arteries.

When the vessel has a solitary dominant feeding vascular pedicle, I tend to be fairly aggressive. I typically use either a partition model (resin) or MIRD (medical internal radiation dose) model (glass) for dosimetry to calculate a target Gy to the lesion. In addition, given the typically large dose needed for this case, I would favor the use of antireflux catheters to maximize delivery into the target tumor and eliminate delivery to adjacent noncancerous tissue. A single vascular pedicle to the tumor such as this provides a unique opportunity to perform a Y-90 "ablative" technique to achieve complete necrosis.

In a patient with a similar lesion and involvement of segment 4 who is a candidate for extended hepatic resection, what approach do you use to induce left hepatic hypertrophy?

Prof. Jakobs: Preservation of an adequate future liver remnant is the principal limitation to liver surgery in patients with primary or secondary liver malignancies. Because segment 4 reveals tumor involvement in this particular case, portal vein embolization (including segment 4) or portal vein ligation does not appear to be the treatment of choice. TARE provides effective treatment of ipsilateral liver tumors, along with introduction of hypertrophy of the contralateral liver lobe. Furthermore, TARE may be associated with a reduced risk of tumor progression compared to portal vein embolization, because the tumor received effective treatment.

Dr. Westcott: First, calculate liver volumes. If it is cirrhotic and the future liver remnant is not at least 30% (40% is preferable at our institution), then proceed with right portal vein embolization. Within 3 to 4 weeks, the future liver remnant typically adequately increased in order to perform a resection. TARE may also cause atrophy with contralateral hypertrophy, but with a time course that is longer than portal vein embolization.

Dr. Arepally: Our practice and surgeons still favor the use of portal vein embolization for the induction of contralateral lobe hypertrophy. Although we have performed radiation lobectomy approaches for hepatic resection, the increased time frame for generating hypertrophy with this method has limited adoption in our clinical practice. ■

1. Garin E, Rolland Y, Lenoir L, et al. Utility of quantitative Tc-MAA SPECT/CT for yttrium-labelled microsphere treatment planning: calculating vascularized hepatic volume and dosimetric approach. Int J Mol Imaging. 2011;2011:398051.
2. Ward TJ, Tamrazi A, Lam MG, et al. Management of high hepatopulmonary shunting in patients undergoing hepatic radioembolization. J Vasc Interv Radiol. 2015;26:1751-1760.
3. Cohen SJ, Konski AA, Putnam S, et al. Phase I study of capecitabine combined with radioembolization using yttrium-90 resin microspheres (SIR-Spheres) in patients with advanced cancer. Br J Cancer. 2014;111:265-271.
4. Raut CP, Boucher Y, Duda DG, et al. Effects of sorafenib on intra-tumoral interstitial fluid pressure and circulating biomarkers in patients with refractory sarcomas (NCI protocol 6948). PLoS One. 2012;7:e26331.
5. Tong RT, Boucher Y, Kozin SV, et al. Vascular normalization by vascular endothelial growth factor receptor 2 blockade induces a pressure gradient across the vasculature and improves drug penetration in tumors. Cancer Res. 2004;64:3731-3736.

MODERATORS:

David M. Liu, MD, FRCPC, FSIR
Vancouver Imaging
Clinical Associate Professor
Faculty of Medicine
University of British Columbia
Vancouver, British Columbia, Canada
Disclosures: Consultant to Sirtex Medical and BTG.

Ripal Gandhi, MD, FSVM
Miami Cardiac and Vascular Institute
Associate Clinical Professor
FIU Herbert Wertheim College of Medicine
Miami, Florida
Disclosures: Proctor for Sirtex Medical.

PANELISTS:

Aravind Arepally, MD, FSIR
Division of Interventional Radiology
Piedmont Radiology
Atlanta, Georgia
Disclosures: Consultant, Surefire Medical; research support, Sirtex Medical.

Tobias F. Jakobs, MD
Associate Professor of Radiology
Head, Clinic of Diagnostic and Interventional Radiology
Hospital Barmherzige Brueder
Munich, Germany
Disclosures: Consultant and speaker for Sirtex Medical Europe and BTG; speaker for Siemens Healthcare.

Mark Westcott, MD
Lenox Hill Hospital
Assistant Professor
Hofstra-Northwell Medical School
New York, New York
Disclosures: Proctor and speaker for Sirtex Medical.