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Treatment planning part I: Vascular considerations associated with safety and efficacy in radioembolization

RAY BRADFORD AND J. MARK MCKINNEY

3.1 INTRODUCTION

Yttrium-90 (\(^{90}\)Y) radioembolization is delivered via arterial supply to the liver. Hepatic neoplasms receive greater than 80% of their perfusion from the hepatic arteries, while the normal hepatic parenchyma receives the majority of its blood supply from the portal vein. This differential blood supply allows for the arterial delivery of relatively large radiation doses to the tumor with relative sparing of normal liver parenchyma (Welsh et al., 2006). \(^{90}\)Y radioembolization for primary and/or secondary neoplasms of the liver necessitates a thorough understanding of hepatic arterial anatomy to ensure safety and efficacy. The interventionalist must be aware that variations in the arterial supply to the liver are common and that these anatomic variations affect both hepatic lobes.

The arteries perfusing the liver also supply many other important visceral structures including the stomach, duodenum, esophagus, pancreas, gallbladder, and abdominal wall. Consideration must be given to protection against nontarget embolization of these extrahepatic visceral structures. Nontarget embolization is avoided during radioembolization with several techniques, such as adjusting the catheter tip location, employing antireflux catheters, and/or using protective embolic redistribution of arterial flow.

In addition to the classic and variant arterial vascular supply to the liver, the interventionalist must take into account extrahepatic arterial parasitization, which occurs with large or peripheral hypervascular neoplasms. Extrahepatic arteries are parasitized from multiple vascular distributions in proximity to the liver parenchyma. Effective \(^{90}\)Y radioembolization may require catheter-directed therapy to these nonhepatic arterial distributions.
Arterial delivery of $^{90}$Y radioembolization requires both training and experience because anatomic treatment decisions are often complex and can be complicated by anatomic variations, extent of disease, and prior treatments. This chapter is not meant to cover every detail of all vascular aspects related to radioembolization, but rather it is meant to provide an overview that can be appreciated and understood by all members of the radioembolization team.

### 3.2 ARTERIAL ACCESS

Interventionalists have the option to approach the hepatic arterial supply via a femoral or radial artery. Femoral artery access is historically the most common access point for diagnostic and therapeutic arterial interventions. However, with the advances of lower profile catheters and the desire to improve patient satisfaction and comfort with early ambulation, radial artery access has become the favored access point for many interventionalists. Prior to radial artery puncture, patency of the ulnar artery and collateral supply through the palmar arch is confirmed utilizing a Barbeau test (Barbeau et al., 2004). The risk of radial artery spasm and thrombosis is mitigated via intra-arterial infusion of heparin, verapamil, and nitroglycerin (Bishay et al., 2014). A Glidesheath is also utilized to minimize trauma to the radial artery. Approaching the celiac artery from a radial artery approach may have anatomic advantages during celiac and hepatic arterial catheter placement. Potential disadvantages to radial artery access include the need to utilize longer catheter delivery systems and ergonomic challenges for the operator.

### 3.3 HEPATIC ARTERIAL ANATOMY

Classic hepatic arterial supply arises from the celiac artery with bifurcation of the proper hepatic artery (PHA) into the right and left intrahepatic arterial branches (Figure 3.1). This classic pattern is estimated to be present in greater than 60% of patients (Covey et al., 2002; Lee et al., 2012). Variations of the right hepatic arterial supply include replaced right hepatic artery (RHA) (12%) and accessory RHA (6%) from the superior mesenteric artery (Covey et al., 2002; Lee et al., 2012). Variations of the left hepatic supply include replacement of the LHA (5%) and accessory LHA (15%) from the left gastric artery (LGA) (Covey et al., 2002; Lee et al., 2012) (Figure 3.2). In addition, a middle hepatic artery may present either as an accessory branch of the RHA or a true trifurcation from the PHA (Kerlan and LaBerge, 2006).

Extrahaepatic arteries are important for the interventionalist utilizing $^{90}$Y radioembolization as locoregional therapy. Extrahaepatic arteries are a potential nontarget pathway for $^{90}$Y to be diverted from the targeted hepatic parenchyma to nontargeted adjacent viscera or musculoskeletal structures. Specific extrahaepatic arteries at risk for nontarget radioembolization typically include the right gastric, gastroduodenal, pancreaticoduodenal, cystic, esophageal, and falciform arteries. Pre-$^{90}$Y radioembolization planning arteriography is utilized to map and discover potential perihepatic arterial pathways that place the patient at risk for nontarget embolization during $^{90}$Y therapy.

The right gastric artery (RGA) frequently arises from LHA, PHA, gastroduodenal artery (GDA), or common hepatic artery (CHA) (VanDamme and Bonte, 1990; Liu et al., 2005). Because both RGA and LGA perfuse the lesser curvature of the stomach, it is important to identify the RGA origin. RGA is characteristically small in caliber and may have a sharply angulated origin.
that makes selective catheterization challenging. When the RGA origin cannot be identified, it is frequently evaluated via a left gastric arteriogram (Figure 3.3).

The gastroduodenal artery is a relatively large artery arising from the CHA and supplies the pancreas, duodenum, and greater curvature of the stomach via the pancreaticoduodenal arcade and gastroepiploic arteries (Figure 3.1). The risk of nontarget embolization to the gastroduodenal artery must be evaluated due to its continuity with the PHA and the subsequent bifurcation of the PHA into the RHA and LHAs. Depending on treatment intent and catheter tip location for $^{90}$Y radioembolization, the gastroduodenal artery may not be at significant risk.

The cystic artery perfuses the gallbladder and typically originates from the proximal RHA.
Clinical symptoms from radioembolic cholecystitis can occur but are usually self-limiting.

Specific attention to the intrahepatic arterial distribution is important for evaluating several extrahepatic arterial perfusion pathways. One of these intrahepatic-to-extrahepatic arterial pathways is the falciform artery, which arises from the left or middle hepatic arteries and perfuses the anterior abdominal wall (Figure 3.4) (Baba et al., 2000; Liu et al., 2005). Other extrahepatic artery pathways that can complicate radioembolization include the esophageal and gastric branches arising from the LHA (Figure 3.5) and the duodenal branches arising from the central hepatic arteries. With careful analysis, these extrahepatic arterial pathways can be identified and strategies can be developed to protect against nontarget $^{90}$Y radioembolization.

Some posttreatment examples of $^{90}$Y nontarget embolization through extrahepatic arteries are shown in Chapter 13, associated with clinical sequelae discussed in Chapter 14.

### 3.4 COMPLICATED HEPATIC ARTERIAL ACCESS

Diffuse or focal vascular disease may be a complicating factor regardless of whether the interventionalist utilizes a femoral or radial arterial approach. Severe peripheral vascular disease with atherosclerotic stenosis of the aorta or iliac arteries may require a contralateral femoral artery approach or radial artery approach. Prior to choice of arterial access, the interventionalist should also be aware of the patient’s prior surgical history, which may include aortic, iliac, femoral, or upper extremity surgical grafts.

Celiac artery stenosis from median arcuate ligament syndrome (Figure 3.6) or atherosclerosis...
may be encountered as a complicating access issue. Stenosis from median arcuate ligament syndrome is often incomplete and allows coaxial microcatheter advancement from an access catheter seated in the narrowed celiac artery. Ultimate relief of median arcuate ligament syndrome is surgical release (Columbo et al., 2015). In the case of atherosclerotic celiac artery stenosis or occlusion, celiac artery access for radioembolization can be achieved via celiac artery stent placement.

In the cases where celiac occlusion is complete and celiac catheter access cannot be achieved, enlarged pancreaticoduodenal arterial collaterals from the superior mesenteric artery provide a retrograde approach to hepatic artery $^{90}$Y radioembolization (Figure 3.7). To achieve hepatic artery access via the pancreaticoduodenal collaterals, an access catheter is seated in the superior mesenteric artery and coaxial microcatheter techniques are utilized to advance access serially through the superior mesenteric artery, inferior pancreaticoduodenal trunk, pancreaticoduodenal arcade, gastroduodenal artery, and into the proper and intrahepatic arterial branches. Supraselective access into the hepatic arteries may be limited when taking a circuitous retrograde approach.

Consideration must be given to extrahepatic arterial pathways that may be recruited and parasitized for perfusion of intrahepatic neoplasms. Characteristics that increase the likelihood of parasitization include peripheral and large tumors and prior hepatic arterial embolization (Abdelmaksoud et al., 2011).

Awareness and identification of parasitized extrahepatic arteries is necessary to completely treat targeted tumor beds. Tumors that receive supplemental arterial blood supply from parasitized extrahepatic arteries are particularly at risk of being undertreated (Abdelmaksoud et al., 2011). Bland, conventional chemoembolization, or drug-eluting bead chemoembolization of parasitized extrahepatic arteries supplying peripherally located hepatic tumors provides therapeutic intent and reestablishment of primary hepatic arterial perfusion through intrahepatic arteries. Extrahepatic arteries most commonly recruited for tumor perfusion include the right inferior phrenic, internal mammary, intercostal, right adrenal, right renal, and greater omental arteries (Figure 3.8) (Abdelmaksoud et al., 2011).
Coil embolotherapy is a well-developed technique utilized by interventionalists to occlude and redirect arterial perfusion. Historically, coil embolotherapy is most frequently utilized in the GDA and RGA during planning arteriography to prevent nontarget embolization.

In the early implementation of radioembolization, the gastroduodenal artery was routinely coil embolized at its origin to prevent nontarget embolization. Gastroduodenal artery coil embolization is performed excluding the GDA as a potential pathway for nontarget embolization. However, additional experience with $^{90}$Y radioembolization has shown that gastroduodenal coil embolization is frequently unnecessary and may actually increase the risk of intrahepatic recruitment of duodenal and pancreatic arterial collateral pathways (Hamoui et al., 2013a, 2013b). Avoidance of gastroduodenal coil embolization has been demonstrated to decrease procedure time, contrast volume, and radiation exposure to the patient (Fischman et al., 2014).

**Figure 3.8** Parasitized extrahepatic arteries perfusing intrahepatic tumor (arrowheads). (a) Right inferior phrenic artery. (b) Right internal mammary artery. (c) Intercostal artery. (d) Right adrenal and renal arteries.
The RGA is at a particular risk for nontarget radioembolization due to its proximity to typical radioembolization catheter tip locations. The RGA originates from either the LHA, PHA, GDA, or CHA (Covey et al., 2002; Lee et al., 2012). The RGA is often very small in caliber and has a sharply angulated origin. When technically possible, the RGA is directly accessed via a coaxial microcatheter and its origin is coil embolized. When the RGA cannot be identified or accessed directly, it may be successfully approached via retrograde access from the LGA. An access catheter is seated in the LGA origin, and a coaxial microcatheter is advanced along the communicating artery from the left gastric to the RGA origin where coils are carefully deposited. If $^{90}$Y catheter tip delivery does not pose a risk to the RGA, then coil embolization is not necessary (Hamoui et al., 2013a, 2013b).

Coil embolization is also utilized to protect other extrahepatic arterial beds such as the falciform artery. If a falciform artery is identified (Figure 3.4), coil embolization of the falciform artery is performed when technically possible because $^{90}$Y radioembolization to the falciform artery can result in a highly localized midabdominal burning sensation for a period of days or weeks (Liu et al., 2005). When the falciform artery cannot be accessed, studies have shown that ice packs to the anterior abdominal wall provide vasoconstriction that reduces nontarget embolization to the terminal falciform arterial branches (Wang et al., 2013).

Coil embolization is also applied when esophageal or gastric branches are identified as originating within the intrahepatic arterial supply. Branches to the esophagus and stomach may originate from the LHA and are embolized to prevent nontarget embolization (Figure 3.5).

Antireflux catheteres have been devised to minimize nontarget embolization during radioembolization (Figure 15.2). Catheters are designed to deliver $^{90}$Y microspheres in target hepatic arteries ranging from 2 to 6 mm in diameter. Studies have demonstrated increased tumor uptake and decreased nontarget embolization in multiple tumor types (Pasciak et al., 2015). A prospective randomized study of protective embolic coiling versus antireflux catheter delivery demonstrated reduced fluoroscopy time, procedure time, and contrast dose during the planning arteriogram phase because the need for coil embolotherapy is eliminated or reduced (Fischman et al., 2014).

3.7 TECHNIQUES TO MINIMIZE HEPATOPULMONARY SHUNTING

Hepatopulmonary shunting may lead to nontarget pulmonary embolization and must be recognized during planning and treatment with $^{90}$Y radioembolization. Hepatopulmonary shunt fraction is usually evaluated with a test dose of technium-99m microaggregated albumin ($^{99m}$Tc-MAA) during the arterial planning phase of $^{90}$Y treatment, as described in Chapter 4. Arteriovenous shunting into the hepatic veins and portal veins is common with liver tumors (Figure 3.9) (Sugano et al., 1994; Chan et al., 2010). $^{90}$Y microspheres can travel to the pulmonary arterial bed via the hepatic and portal veins. Excessive hepatopulmonary shunting with $^{90}$Y microspheres may in rare cases lead to radiation pneumonitis. Radiation pneumonitis manifests clinically with nonspecific symptoms of fever, nonproductive cough, and dyspnea.

Figure 3.9 Arteriovenous shunting from hypervascular hepatocellular carcinoma leads to early opacification of the draining hepatic vein (arrowheads).
Radiation pneumonitis is radiographically suggested as peribronchial cuffing on chest imaging (Graves et al., 2010) and as a restrictive pattern on pulmonary function testing. Treatment is inhaled and/or systemic corticosteroids (Leung et al., 1995). Ultimately, radiation pneumonitis can lead to debilitating chronic disease.

Because of the potential risks of an elevated pulmonary shunt fraction leading to radiation pneumonitis, manufacturers have released guidelines for ⁹⁰Y microspheres. The resin ⁹⁰Y microsphere training manual guidelines by Sirtex Medical (North Sydney, Australia) recommend a lung radiation dose limit of 25 Gy per treatment session, not to exceed a 50 Gy cumulative dose. For glass ⁹⁰Y microspheres, the package insert by BTG International (West Conshohocken, Pennsylvania) recommends an upper limit of 16.5 mCi delivered to the lungs. Ho et al. (1997) also recommend restricting the lung radiation absorbed dose to <30 Gy. Dose reductions for an elevated hepatopulmonary shunt fraction have been shown to result in reduced efficacy of ⁹⁰Y radioembolization therapy (Garin et al., 2015; Lam et al., 2015). However, studies have shown that the risk from an elevated hepatopulmonary shunt fraction is very low. In one series, no patients were found to have radiation pneumonitis with a cumulative lung dose >30 Gy (Salem et al., 2008). Additional considerations associated with hepatopulmonary shunt will be discussed in Chapter 4.

Several non–dose-reducing techniques have been utilized to deal with high hepatopulmonary shunt fraction. The use of systemic sorafenib treatment has been shown to reduce hepatopulmonary shunt fraction by 62%–87% (Theysohn et al., 2012). Transarterial chemoembolization has resulted in reduction of hepatopulmonary shunt fraction by 25%–57% (Rose and Hoh, 2009; Gaba and Vanmiddlesworth, 2012). The use of sorafenib or transarterial chemoembolization may delay ⁹⁰Y radioembolization; therefore, catheter-based techniques to reduce shunting have been developed for use during ⁹⁰Y radioembolization rather than reducing the treatment dose. Catheter-based techniques include temporary balloon occlusion of the hepatic veins or portal veins (Bester and Salem, 2007; Murata et al., 2009), embolization of varices, or bland embolization of the hepatic tumor immediately before or following ⁹⁰Y radioembolization (Ward et al., 2015).

Ward et al. (2015) now recommend that if the expected lung dose is <30 Gy, no shunt mitigation is required. For expected lung dose >30 Gy, catheter-based techniques can be utilized without delay to minimize nontarget radioembolization to the pulmonary arterial bed (Ward et al., 2015).

### 3.8 COMPLICATIONS

Complications from ⁹⁰Y radioembolization have been reported in multiple studies. Early complications include fatigue, pain, nausea, emesis, and low-grade fever. This constellation of early symptoms is typically called postembolization syndrome (Riaz et al., 2009). Postembolization syndrome is usually self-limited and gradually resolves over the first 1–2 weeks of treatment.

Late complications of ⁹⁰Y radioembolization include gastrointestinal ulceration, cholecystitis, pancreatitis, biliary injury, and radiation-induced liver disease (Hamoui and Ryu, 2011), as well as pneumonitis. Gastrointestinal ulceration typically presents weeks after radioembolization as refractory abdominal pain, nausea, and vomiting. Gastrointestinal symptoms may be treated with proton pump inhibitors and sucralfate. Endoscopy may be utilized to confirm the diagnosis of ulceration. Biopsy of the ulcers will often show microspheres in the biopsy specimen.

Radiation-induced liver disease typically occurs 4–8 weeks after radioembolization with elevation of alkaline phosphatase and bilirubin. Radiation-induced liver disease is a clinical diagnosis associated with ascites and jaundice (Sangro et al., 2008; Hamoui and Ryu, 2011). Multiple prior chemotherapy regimens are a risk factor for radiation-induced liver disease. Dosimetric thresholds related to radiation-induced liver disease are discussed in Chapter 5.

Biliary sequelae following ⁹⁰Y radioembolization are usually clinically inconsequential. As with other liver-directed therapies, biliary complications are seen more commonly with secondary neoplasms than with hepatocellular carcinoma. Potential biliary complications included stricture formation, obstruction, biloma, cholecystitis, hepatic abscess, and serum bilirubin toxicity. Patients are often asymptomatic, even with imaging evidence of biliary complications. Treatment
for biliary sequelae is based on clinical presentation and may include antibiotics, percutaneous drainage of fluid collections, biliary decompression, and cholecystectomy (Atassi et al., 2008). Additional discussion of the late complications of radioembolization, including identification using advanced imaging techniques, can be found in Chapters 13 and 14.

3.9 ANGIOGENESIS

Tumor growth and spread is known to be driven by a complex interplay of proangiogenic and antiangiogenic cytokines (Bergers and Benjamin, 2003). Since some patients experience early tumor recurrence following 90Y radioembolization, it is important to consider the role that cytokines may play. Vascular endothelial growth factor (VEGF) levels are known to be associated with suboptimal outcomes in primary and secondary liver neoplasm. In addition, VEGF is associated with hepatocellular carcinoma disease stage, presence of metastasis, vascular invasion, treatment response, and overall survival (Xiong et al., 2004; Sergio et al., 2008). Carpizo et al. (2014) found that VEGF, angiopoietin-2 (Ang-2), platelet-derived growth factor subunit BB (PDGF-BB), and other nonclassic cytokines were temporally associated with 90Y radioembolization. They observed spikes in the cytokine baseline values as sampled following first- and second-stage 90Y radioembolization treatment episodes. This evidence suggests that 90Y radioembolization has the potential to upregulate angiogenic cytokines. When overall survival (OS) is evaluated in correlation with cytokine release, there is correlation between shortened OS and temporal spikes in VEGF, Ang-2, and PDGF-BB. These cytokines appear to affect OS by promoting angiogenesis. It is plausible that some patients might benefit from antiangiogenic therapy administered before 90Y radioembolization (Carpizo et al., 2014).

3.10 CONCLUSION

Vascular considerations are an important part of 90Y radioembolization planning and therapy. From choosing arterial access to understanding and planning for variations of normal hepatic arterial anatomy, considerable thought must be given to each specific patient’s situation. Unexpected complicating factors such as stenotic or occluded celiac access, extrahepatic arterial communications, parasitized arterial perfusion, and hepatopulmonary shunting are frequently encountered. Techniques such as coil embolization, antireflux catheters, and dose modifications allow for safe and efficacious delivery of yttrium-90 to primary and secondary hepatic neoplasms.

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