Hepatic Resection in the Era of Liver-Directed Therapies

What every interventional radiologist and surgeon needs to know.

BY JOHN J. PARK, MD, PHD, AND JONATHAN KESSLER, MD

Over the last decade, there have been dramatic increases in the use of transarterial embolotherapies for the treatment of hepatic malignancies. Although palliative treatments remain the main driving force behind this trend, part of the increased utilization is the result of expanding indications. Increasingly, transarterial therapies are being performed in the neoadjuvant and adjuvant settings, to downstage tumors, bridge patients to liver transplant, and improve postoperative survival. Over this same period of time, advances in pre- and postoperative management, as well as surgical techniques, have expanded the number of patients who can benefit from surgical resection. As the concomitant use of liver-directed therapies and surgical resection continue to evolve, it is imperative that both the interventional radiologist and surgeon understand the implications of patients sequentially undergoing each treatment modality. This article briefly explores the sequential use of transarterial therapies before and after major liver resection.

TRANSARTERIAL THERAPY BEFORE LIVER RESECTION

Surgical resection and ablation are considered the treatments of choice for most resectable liver cancers. Although the role of neoadjuvant transarterial chemoembolization (TACE) in the setting of resectable tumors has been explored with an abundance of data verifying its safety and efficacy, this role remains controversial and not widely adopted,[1] as no clear survival benefit has been proven in this setting. For the majority of patients, surgery is not initially an option for a variety of reasons, including advanced tumor stage, significant comorbidities, inadequate future liver remnant (FLR), or poor performance status. Furthermore, certain patients are deemed unresectable due to the size or location of their hepatic tumors.

This subset of patients may potentially be resectable or eligible for transplantation if their tumors can be adequately downsized.[2,3] As early as 1993, Yu et al demonstrated the benefits and safety of performing surgery

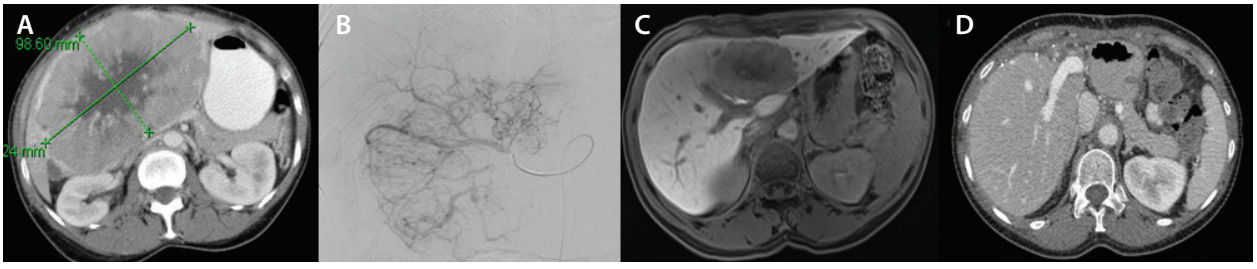


Figure 1. Hepatic resection following tumor downstaging with TACE. Contrast-enhanced CT demonstrating one (of two) large, left liver lobe hepatomas (A). Angiogram obtained during the first TACE procedure out of five total procedures (B), with final follow-up Eovist MRI (Bayer HealthCare; 20-minute delay) demonstrating a marked decrease in tumor sizes (C). Portal venous CT following curative extended left hepatectomy with right liver remnant (D).

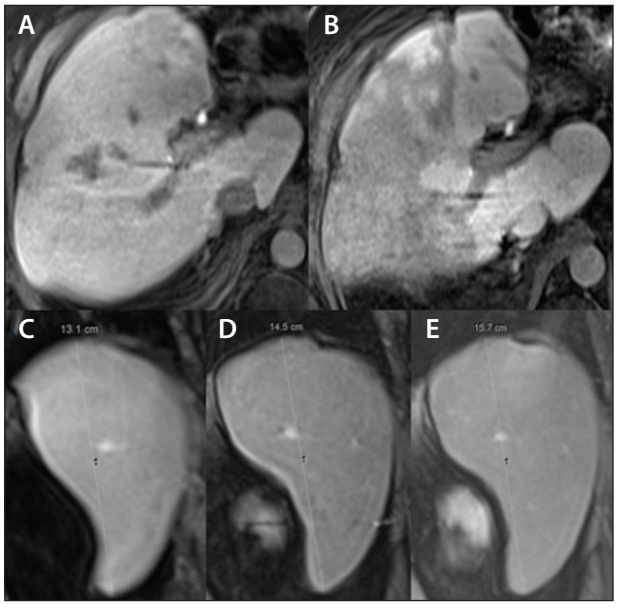


Figure 2. Pre– and post–Y-90 selective internal radiation therapy (SIRT) with apparent hepatic fibrosis and splenomegaly. Eovist MRI during the hepatobiliary phase before Y-90 SIRT (A) and at 4-month follow-up after Y-90 SIRT (B) demonstrating new areas of band-like signal abnormality. Serial preprocedure (C) and 1- and 4-month (D, E, respectively) postprocedure images of the spleen showing progressive splenic enlargement after Y-90 SIRT.

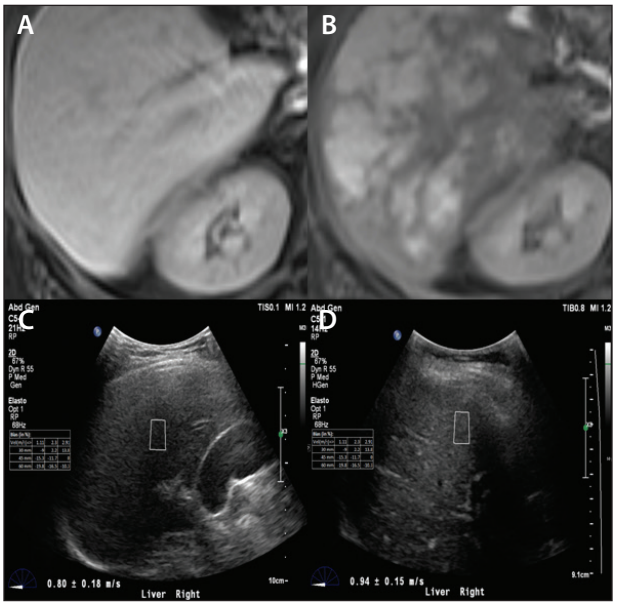


Figure 3. MRI and ultrasound point shear wave elastography (PSWE) after Y-90 SIRT. Eovist MRI before and after Y-90 SIRT demonstrating prominent fibrotic changes following right liver lobar radioembolization (A, B). Ultrasound-based PSWE within the areas of apparent fibrosis on MRI before and after Y-90 SIRT (C, D). No significant changes were apparent in fibrosis indices before and after the procedure, despite the robust appearance of bridging fibrosis on MRI (PSWE mean cutoff values, 2–4.5 kPa for METAVIR F0 [normal]; 4.5–5.7 for F0–F1 [normal to mild]; 5.7–12 for F2–F3 [mild-moderate]; 12–21+ for F3–F4 [moderate-severe]).

following downstaging with chemoembolization.[4] In this study, they described the development of adhesions along the diaphragm and thickening of the gallbladder wall and hepatoduodenal ligaments after chemoembolization. However, these findings did not result in additional complications during subsequent surgeries. Moreover, with decreased tumor sizes and increased necrosis, many previously unresectable patients who subsequently underwent chemoembolization became resectable and were able to proceed to hepatic resection.

Chemoembolization is now considered a safe and viable option to control or downstage liver cancers prior to surgical resection and/or "bridge" to transplantation, prominently being incorporated in many staging and treatment guidelines, including the Barcelona Clinic Liver Cancer and Hong Kong Liver Cancer staging systems for hepatocellular carcinoma (HCC) and National Comprehensive Cancer Network guidelines for liver-dominant metastatic diseases.[5-7] Figure 1 shows a patient with initially unresectable HCC that was successfully downstaged with TACE and subsequently treated with curative major surgical resection.

Similar to chemoembolization, transarterial radioembolization (TARE) has successfully been used to treat both primary and secondary liver cancers. However, surgical resection after TARE has been slow to gain mainstream acceptance. One reason for this reluctance is the concern for radiation exposure by the surgical team after radioembolization. With a relatively short half-life ($t_{1/2,}$ = 64.1 h) and limited range of the β particles (11 mm; mean distance of 2.5 mm), direct exposure to most of the potent effects of the yttrium-90 (Y-90) β radiation can be mitigated by both time and distance in patients requiring surgery within the immediate post-implantation time frame. Other than the risk of direct radiation exposure to the surgical team, a more practical concern is the potential direct and secondary postradiation effects of the radioembolization treatment on the liver itself, which could include histologic liver fibrosis, portal hypertension with splenomegaly, and hepatic volume changes (Figure 2).[8]

Although liver biopsy remains the "gold standard" for evaluating liver fibrosis, it is invasive and limited by sampling errors. Recently, other noninvasive tools, such as real-time shear wave elastography, have been shown to accurately assess liver fibrosis by measuring liver "stiffness."[9] In order to evaluate radioembolization-induced

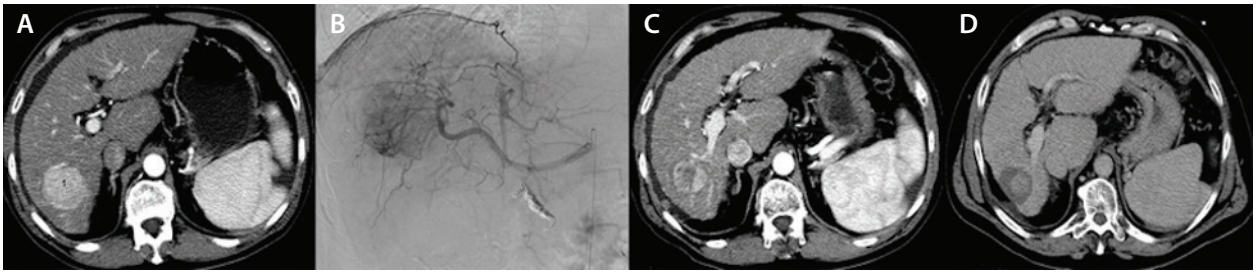
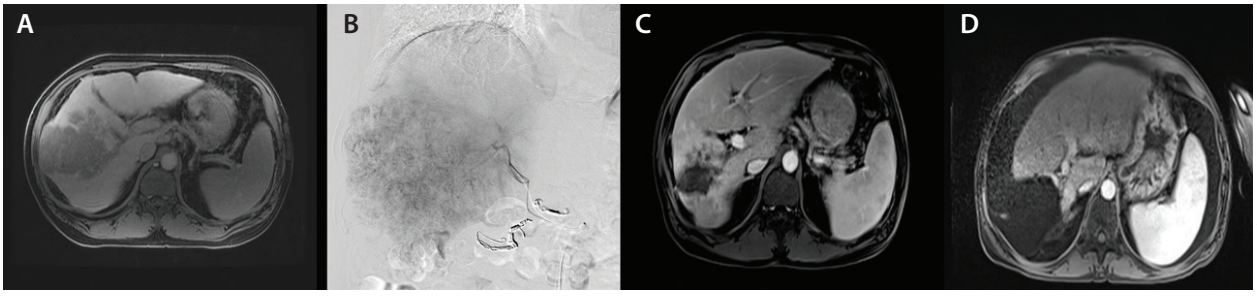


Figure 4. Right liver HCC successfully downstaged with Y-90 SIRT and treated with curative microwave ablation. Arterial phase CT with a large, hypervascular right liver HCC (A). An angiogram was obtained during selective right segmental radioembolization (radiation segmentectomy) (B) with follow-up after Y-90 contrasted-enhanced CT demonstrating an interval decrease in tumor size and increase in necrosis (C). A 1-year follow-up CT was performed after radioembolization and curative microwave ablation of the tumor, showing no evidence of recurrent disease (D).

liver fibrosis, a recent study utilizing ultrasound shear wave elastography demonstrated that liver segments undergoing radioembolization were slightly stiffer or fibrotic at 3 months after Y-90 treatment (mean shear wave elastography, 17.4 kPa) compared with baseline (mean shear wave elastography, 7 kPa). These and other findings have led some in the surgical field to caution hepatic resection following radioembolization with emphasis on the need for careful patient selection in this population.[10,11]

Our group is currently evaluating the long-term effects of Y-90 radioembolization on inducing liver fibrosis using sequential ultrasound-based elastography in order to track potential radiation-induced liver changes. However, despite the appearance of fibrosis on MRI after Y-90 use, in our experience, this finding does not appear to correlate with significant increases in liver stiffness by point shear wave elastography (Figure 3). Nevertheless, despite these concerns of developing hepatic fibrosis and subsequent portal hypertension, many other studies have demonstrated that patients can safely undergo liver ablation, surgery, and transplantation after radioembolization without significant increases in complications.[12,13]

Figures 4 and 5 illustrate cases in which patients were initially treated with Y-90 radioembolization of their liver tumors followed by successful percutaneous ablation (Figure 4) or surgical resection (Figure 5). To further evaluate the implications of radioembolization prior to surgery, Pardo et al recently presented their findings from the multicenter, retrospective Post-SIR-Spheres Surgery study (also known as P4S), which evaluated the outcomes of liver resection or transplantation after radioembolization.[14] A total of 100 patients were evaluated, with 71 patients undergoing liver resection and 29 patients undergoing transplantation after Y-90 SIRT. Overall, despite many patients having previously undergone liver-directed therapies (70.5% in the resection arm and 68.9% in the transplant arm) or previous systemic therapies (50% in the resection arm and 3.4% in the transplant arm), major complications were similar to previously published reports with the exception of patients undergoing extended liver resections. The group undergoing extended liver rejections (trisegmentectomies either by conventional means or by ALPPS [associating liver partition and portal vein ligation for staged hepatectomy] procedure) had the highest rate of post-



Courtesy of Dr. Paola Devis, University of Arizona.

Figure 5. Right liver hepatoma successfully downstaged with Y-90 SIRT and treated with curative resection. An MRI showing a large, right liver HCC (A), which was initially treated with right lobar radioembolization (B). Contrasted-enhanced MRI after Y-90 demonstrating interval decrease in tumor size with contralateral hypertrophy (C). Contrast-enhanced MRI following successful resection of the downstaged liver mass with no evidence of recurrent disease (D).

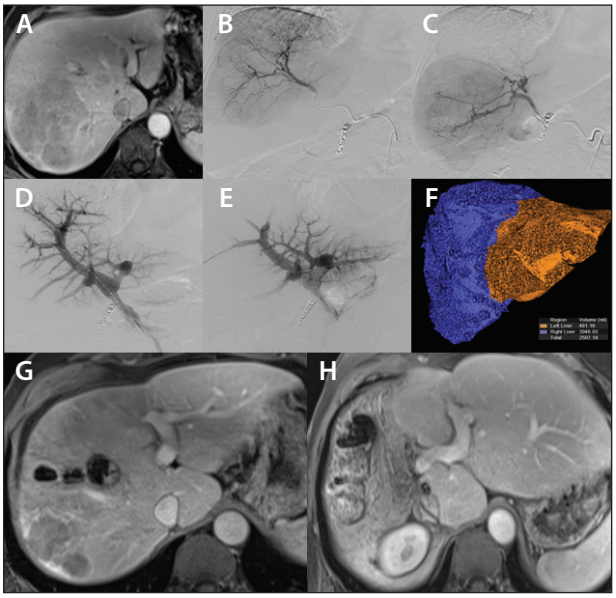


Figure 6. Multifocal HCC within the right liver lobe with small left FLR. Gadolinium-enhanced MRI demonstrating bulky right lobar disease and small FLR (A). Y-90 SIRT of the right liver tumors (bridging therapy) was performed using split doses via the main right hepatic artery (B) and replaced right hepatic artery (C). The patient subsequently underwent PVE following Y-90 SIRT, with transhepatic, transportal venograms depicted pre-PVE (D) and post-PVE (E). Volume-rendered three-dimensional reconstruction with volumes (inset) showing hypertrophy of the FLR (F). Eovist MRI after Y-90 SIRT and PVE demonstrating decreased tumor burden within the right liver lobe and interval hypertrophy of the FLR (note the magnetic artifact from the embolic material placed during PVE) (G). Final image after successful resection of diseased right liver lobe with marked hypertrophy of the left liver remnant (H).

surgical complications (36.8% developed grade ≥ 3 liver failure; $P < .001$), including all four of the study-related mortalities.

It is unclear if the higher rate of major complications and mortality in the extended resection group was directly related to the addition of radioembolization in these heavily pretreated patients because there was no comparative group of surgically resected patients who did not receive prior TARE treatment. Furthermore, it is possible that morbidity and mortality may also be related to the relatively invasive ALPPS procedure, which involves surgical portal vein ligation and two-staged hepatectomy to induce contralateral hepatic hypertrophy. Nevertheless, this study suggests that patients can safely proceed with major resections and transplantations without any significant additional risks of complications after liver radioembolization.

PORTAL VEIN EMBOLIZATION AND TRANSARTERIAL THERAPIES

Many patients who are surgical candidates may not often proceed to resection due to inadequate FLRs. In these patients, portal vein embolization (PVE) is often performed prior to ipsilateral hepatectomy in order to promote contralateral hypertrophy, resulting in a viable FLR. However, in cases of rapidly progressing liver tumors, waiting the 4 to 6 weeks it takes to achieve optimal hypertrophy of the contralateral liver may not be feasible due to rapid tumor progression, resulting in liver failure and/or development of increased contralateral tumor burden. In these patients, combined PVE with transarterial, liver-directed therapy may play a pivotal role in both promoting contralateral hypertrophy and stabilizing or downstaging the ipsilateral disease progression. Despite this aggressive combined approach, a few groups have shown that surgical resection following combined PVE and TACE can safely be performed in carefully selected patients.[15,16] Bouazza et al recently demonstrated in a single case study that liver resection was also safely performed in a patient who underwent both PVE and TARE.[17] Our own experience has also shown this combined approach to be safe and effective (Figure 6); however, despite these small yet encouraging results, additional studies are certainly needed to determine if surgery can routinely follow combined PVE with TACE/TARE.

TRANSARTERIAL THERAPY AFTER LIVER RESECTION

Liver resection remains the optimal treatment for patients with resectable primary and secondary liver malignancies. Unfortunately, 30% to 70% of patients may develop recurrent disease in their liver after curative intent surgery.[18] Patients with recurrence after surgery may still have liver-confined disease and potentially benefit from additional transarterial liver-directed therapies. However, major liver surgery can result in a variety of anatomic and physiologic alterations that must be considered prior to transarterial treatment.

The rich collateral arterial supply to the liver and upper gastrointestinal (GI) system has traditionally been an advantage to the interventionist. Prophylactic coil embolization of visceral branches to the stomach, bowel, and pancreas are often performed to limit the risk of nontarget treatment. Typically, end-organ perfusion is maintained through the extensive natural collateral pathways that exist in the GI tract. Previous surgery may disrupt these pathways, and collateral reperfusion may no longer be possible. In these settings, additional embolization may result in unintended tissue ischemia

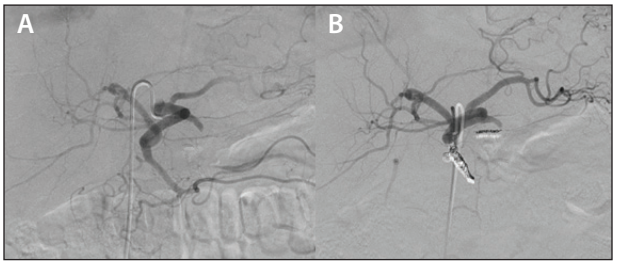


Figure 7. A patient with a metastatic pancreatic neuroendocrine tumor who had previously undergone distal pancreatectomy and splenectomy. These images are from a mapping angiogram prior to radioembolization. A celiac angiogram showing resection of the splenic artery with its pancreatic and gastric branches. The patient has a replaced right hepatic artery. The gastroduodenal artery and right gastric artery arise near the planned treatment zone (A). Following embolization of the right gastric artery and gastroduodenal artery, arterial supply to the gastric body must be reconstituted from the left gastric artery or superior mesenteric artery (B).

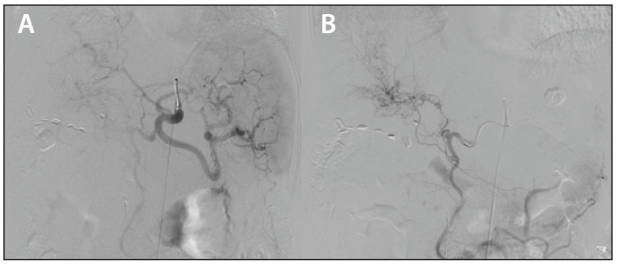


Figure 8. A patient with HCC status after a right hepatic resection with multifocal tumor recurrence. A celiac angiogram demonstrating parasitized arterial supply from the right inferior phrenic artery to a tumor in the hepatic dome (A). Tumor blush is also shown in the right lobe of the liver, near the surgical clips. A gastroduodenal angiogram demonstrates that arterial supply to the tumor in the right lobe of the liver now arises from collateral branches of the gastroduodenal artery (B).

or infarction (Figure 7). Therefore, in the postoperative setting, it is imperative that the interventionist verify collateral perfusion prior to prophylactic embolization of mesenteric vessels.

Additionally, in the nonoperative patient, arterial tumor supply is fairly predictable based on tumor location. When extrahepatic parasitization of blood supply to liver tumors is present, it is typically in the setting of large tumors that abut the liver surface. Furthermore, the supply is typically from predictable vascular territories such as the phrenic (posterior dome), internal mammary (anterior dome), intercostal (posterolateral surface), or supraduodenal (central/medial liver) arteries that supply the adjacent tissue (Figure 8). When the normal hepatic arterial supply has been disrupted by a previous intervention, traditional perfusion of hepatic segments can no longer be assumed, and a variety of hepatic and nonhepatic vessels may be recruited to perfuse the liver tumor.

Interventionists must be aware of these alterations to maximize their ability to deliver a therapeutic dose to the liver and limit the chance of nontarget embolization. In our practice, we typically advocate the utilization of cone-beam CT with multiplanar reformations and coronal maximum-intensity projections (25-mm thickness) in all patients who have previously undergone hepatic surgery to confirm the arterial supply to the tumor and the absence of extrahepatic perfusion.

Normal hepatic function may also be compromised following major liver resection. Although many patients go on to develop significant liver remnant hypertrophy, a subset of patients may have chronic diminished liver function. Typically, this is seen in patients with underlying cirrhosis or those who have undergone systemic chemotherapy. Further liver-directed therapies in this population could result in increased liver toxicity or potentially failure. Although this population should be approached with caution, recent analyses by our group and others support the fact that liver-directed therapy with radioembolization after liver resection is safe and does not result in any increased short-term toxicity if patients are carefully selected.[19,20]

Finally, although salvage transarterial therapy after liver resection can certainly offer benefits to patients with recurrent disease, the question remains whether selected subsets may benefit more from early intervention. Recently, several groups have started to investigate whether early transarterial therapy after liver resection may actually lower the chance of postoperative recurrence and improve patient outcomes. Much akin to adjuvant systemic chemotherapy after surgical resection, these early studies have sought to identify whether postoperative chemoembolization may offer a benefit to patients who undergo hepatic resection for HCC.

Sun et al studied 322 patients who underwent R0 hepatic resection for HCC with pathologic evidence of microvascular invasion. One hundred thirty-seven of these patients underwent postoperative TACE. The 5-year overall survival rates were significantly increased in those who underwent TACE (54% vs 43%; $P = .006$).[21] Li et al investigated a cohort of patients with more advanced HCC, presenting with macrovascular portal vein involvement. Patients in this study were randomized to surgery alone, surgery and TACE, or surgery/TACE/portal vein

chemotherapy. In this study, disease-free survival rates were significantly improved in the group that underwent surgery, TACE, and portal venous chemotherapy.[22]

CONCLUSION

As the combined use of liver-directed therapies along with hepatic surgery continues to increase, there are many considerations that both the interventional radiologist and the surgeon need to be aware of in order to ensure safety and efficacy. Through meticulous patient selection and understanding the implications of combining these platforms, one should be able to treat with liver-directed therapies either before or after surgical resection without expecting any increase in complications. ■

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