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Yttrium-90 Radioembolization: Current Clinical Practice and Review of the Recent Literature

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A B S T R A C T

Curative options for the treatment of primary or secondary hepatic malignancies are transplant and surgical resection. Transplant and surgical resection offers the best clinical outcome; however, it is only available to a limited number of patients who present with early-stage disease. For patients beyond curative resection or outside transplant criteria, locoregional therapies remain an excellent treatment option. Yttrium-90 (^{90}Y) radioembolization is a transarterial catheter–based technique that is increasingly being used in the management of primary and secondary liver malignancies. The focus of this article is to discuss the use of ^{90}Y radioembolization for the treatment of unresectable hepatic malignancies along with a review of the relevant literature.

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver. In 2012, 14 million cases were reported worldwide, and this number is predicted to grow to 22 million over the next 2 decades. HCC is the sixth most common malignancy worldwide and has become the second most common cause of cancer-related death in the world and seventh most common cause in the United States (Ghouri et al., 2017; Hickey et al., 2016; Lee and Khan, 2017). Cholangiocarcinoma is the second most common primary tumor of the liver. Furthermore, many tumors can metastasize to the liver including colorectal cancer, neuroendocrine tumors, breast cancer, and ocular melanoma. Unresectable or advanced primary and secondary tumors of the liver are challenging to treat because of the limited survival benefit of systemic chemotherapy (Lewandowski et al., 2011; Padia et al., 2017a; Salem and Lewandowski, 2013; Salem et al., 2011).

Potentially curative options for the treatment of primary or secondary hepatic malignancies are transplant and surgical resection. Transplant and surgical resection offers the best clinical outcome; however, it is only available to a limited number of patients who present with early-stage disease. For patients beyond curative resection or outside transplant criteria, locoregional therapies remain an excellent treatment option (European Association For The Study Of The Liver and European Organisation For Research And Treatment Of Cancer, 2012). For patients with unresectable hepatic malignancies, transarterial embolotherapies include bland transarterial embolization (TAE), conventional transarterial chemoembolization, drug-eluting beads TAE, and selective internal radiation therapy with radioembolization using Yttrium-90 (^{90}Y) (Lee and Khan, 2017).

^{90}Y radioembolization is a transarterial catheter–based technique that is increasingly being used in the management of primary and secondary liver malignancies (Padia et al., 2017a). The focus of this article is to discuss the use of ^{90}Y radioembolization for the treatment of unresectable hepatic malignancies along with a review of the relevant literature.

Yttrium-90

Radioactive ^{90}Y has emerged as an innovative transarterial embolotherapy procedure in interventional radiology to overcome the limitation of liver injury caused by external beam irradiation in the treatment of unresectable HCC. The liver is radiosensitive and has a low tolerance to hepatic radiation from external sources. This sensitivity especially in cirrhotic liver tissue limits the amount of external beam radiation that can be delivered. Radiation doses greater than 35 Gy-40 Gy have resulted in severe radiation hepatitis also known as radiation-induced liver disease (RILD) in as high as

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50% of treated patients (Murthy et al., 2008). The hallmark of RILD includes anicteric ascites, hepatomegaly, and elevated liver enzymes, which can result weeks to months after treatment. Owing to the development of RILD and complications involving the normal liver parenchyma, external beam radiation has limited utility in the treatment of HCC (Ibrahim et al., 2008; Lewandowski et al., 2011; Molvar and Lewandowski, 2015; Salem and Lewandowski, 2013).

^{90}Y is a pure beta emitter with physical half-life of 64.2 hours and decays to stable element zirconium 90. ^{90}Y beta emitting radioactivity is incorporated into glass (TheraSphere, BTG, Ottawa, Canada) or resin (SIR-Spheres, Sirtex, Lane Cove, Australia) microspheres, which range in size from 20 to 60 μm and penetrates downstream tissue 2.5-11 mm from the delivered site of the microsphere. The resin microspheres (20-60 μm in diameter) differ from glass microspheres (20-30 μm in diameter) in that resin microspheres have a lower specific activity, lower specific gravity, and higher number of particles per treatment (Lewandowski et al., 2011; Salem and Lewandowski, 2013).

Eligibility for ^{90}Y Therapy

The most widely accepted staging system for HCC is the Barcelona Clinic Liver Cancer (BCLC) classification. BCLC classifies the stage of disease with treatment options and prognosis prediction. This staging system is based on performance status, Child Pugh scoring, and tumor characteristics to assign staging, treatment, and prognosis. BCLC separates those patients with very early and early disease, who are eligible for curative therapies, from those with intermediate and advanced disease who can potentially benefit from palliative treatment. BCLC criteria recommend locoregional treatment with chemoembolization for intermediate-stage unresectable HCC or intermediate and locally advanced HCC. Radioembolization using ^{90}Y is an alternative transarterial treatment option to chemoembolization, which offers similar survival outcomes, a longer time to tumor progression, and significantly lower toxicity profile compared with chemoembolization (Llovet and Beaugrand, 2003; Llovet et al., 1999, 2003).

For all patients, one of the most important factors in determining eligibility for radioembolization is Eastern Cooperative Oncology Group (ECOG) performance status. Patients presenting with clearly compromised functional status (ECOG >3) are at high risk for rapid onset of liver failure and associated morbidity with treatment. Some patients with limited ECOG performance may still benefit from therapy. A multidisciplinary approach should always be practiced when providing care to patients with HCC, given the complexity of this disease and wide range of treatment options (Hickey et al., 2014, 2016; Lewandowski et al., 2011; Molvar and Lewandowski, 2015).

Indications

There is considerable treatment overlap in the indications and patient selection for transarterial therapy. When considering ^{90}Y for a patient, one should include transarterial chemoembolization (TACE) and ablation in the discussion and select a therapy based on patient characteristics and treatment expectations. Radioembolization may be offered in patients with unresectable HCC, intrahepatic cholangiocarcinoma, and colorectal metastases (Padia et al., 2017a). Radioembolization has also been used in patients with hepatic metastases from ocular melanoma (Eschelman et al., 2013) and breast cancer (Gordon et al., 2016; Saxena et al., 2014). Radioembolization can be performed to prevent tumor progression while awaiting liver transplant as a bridge to transplant in patients with very early to early disease as defined by the BCLC staging criteria (Padia et al., 2017a).

Contraindications

Absolute contraindications for ^{90}Y therapy include a ^{99m}Tc macroaggregated albumin (MAA) scan with significant hepatopulmonary shunting indicating that a dose of >30 Gy would be delivered to the lungs. Additional contraindications include a single infusion or a combined dose of >50 Gy which would place the patient at risk for radiation pneumonitis. The inability to prevent nontarget embolization to the gastrointestinal (GI) tract using catheter-directed infusion of microspheres is the second absolute contraindication as GI-related radiation injuries have been reported to be refractory to medical treatment and can be devastating (Lewandowski et al., 2011; Padia et al., 2017a).

There are several relative contraindications, which include poor baseline liver function, increased total bilirubin levels >2.0 mg/dL, ECOG performance status >3, and significant ascites. Severe radiographic contrast allergy during angiography, uncorrectable coagulopathy, and renal impairment all must be considered in the decision-making to treat (Padia et al., 2017a).

Nursing considerations

From a nursing perspective, preprocedurally the patient should have taken nothing by mouth (NPO) for a minimum of six hours, ensure the appropriate labs including complete blood count, comprehensive metabolic panel, tumors markers if indicated, and coagulation parameters are drawn. A patent IV should be present and anticoagulation medications should be held per institutional guidelines. Vitals including blood pressure, heart rate, and pulse oximetry should be continuously monitored. Electrocardiogram leads should be in appropriate position. The presence of upper and/or lower extremity pulses should be documented. Other considerations include the application of sequential compression devices to the extremities, a patient warming device, and assessing for a contrast allergy. Appropriate steps should be taken to protect staff as well. Double shoe covers, double gloves, and floor drapes should be applied in all cases. Intraoperatively, the patient should be monitored for pain, urine output, changes in oxygen saturation, and intermittent blood sugars.

After the procedure, assessment for a groin hematoma and pulses for lower extremity perfusion is necessary. If a mapping procedure was performed, Tc-99m MAA was injected to determine the safety of ^{90}Y delivery. A single-photon emission computed tomography scan should be completed within 1 hour of injection. This scan determines the dose for ^{90}Y therapy. If the patient received ^{90}Y therapy, the patient should stay in recovery for 2-3 hours after treatment. A Bremsstrahlung scan will be performed to determine the distribution of the microspheres. The accessed extremity should be straight for 2 hours if closed with a device or 4 hours if hemostasis was achieved with manual pressure.

Postoperatively, the patient may experience fever, lethargy, fatigue, nausea, and abdominal pain. Despite these potential side effects, typically patients who receive ^{90}Y therapy are discharged the same day. On discharge, prescriptions are given for a proton pump inhibitor, steroids, antinausea, and pain medications. ^{90}Y microspheres are a source of radioactivity. There is a small amount of radioactivity around the liver. Therefore, if a patient goes to the emergency department within 3 days of ^{90}Y treatment, they should be instructed to tell their treating physician about the recent procedure. All bodily fluids must be properly disposed in the first 24 hours. Patients do not need to restrict close contact with family members. Hands should be washed after using the restroom and any spill should be wiped and flushed. Potential complications after the procedure include gastric or duodenal ulceration, radiation pneumonitis, radiation hepatitis, acute pancreatitis, and acute cholecystitis.

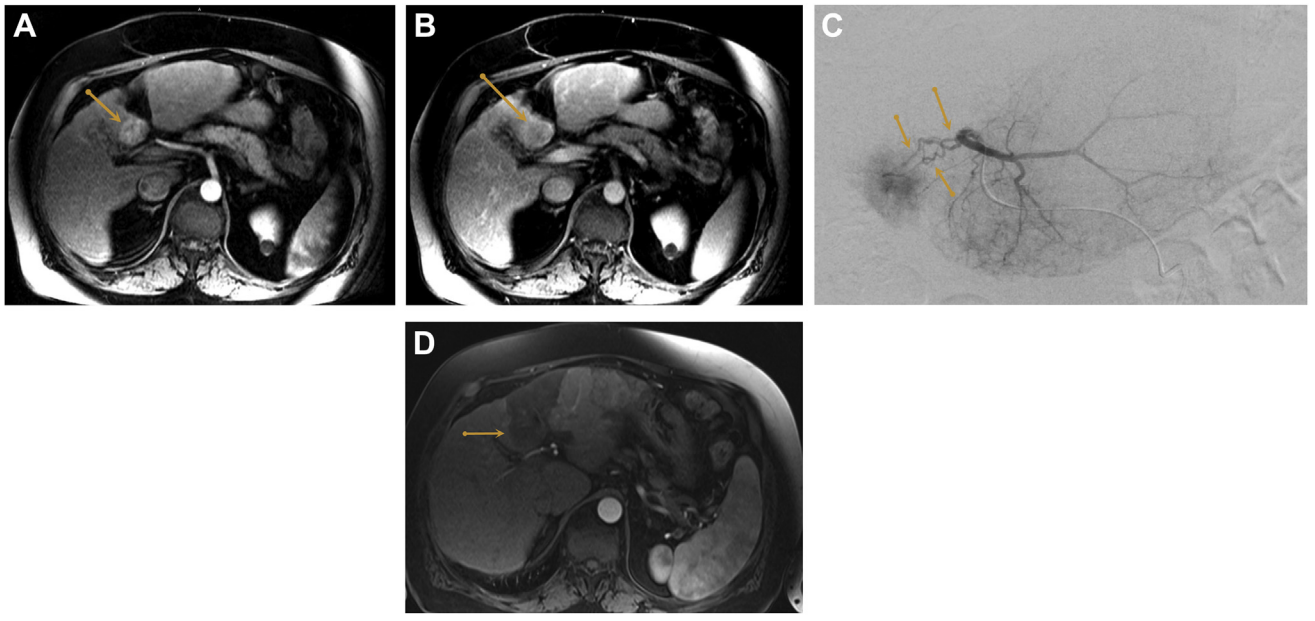

Figure 1. Axial magnetic resonance imaging (MR) T1-weighted images with contrast demonstrate a 3.3 cm mass enhancing in segment 4b demonstrating arterial enhancement (A) and washout on delayed phase (B) (arrows). (C) Catheter angiogram before infusion with ^{90}Y glass microspheres (TheraSpheres) showing arterial supply to the segment 4b tumor (arrows) and a portion of the left hepatic lobe. (D) Posttreatment contrast-enhanced T1-weighted MR images performed 4 months later show complete response without evidence of viable tumor (arrow).

Relevant literature and data

Although treatment of liver tumors with ^{90}Y microsphere radioembolization was described over 30 years ago (Herba et al., 1988), it has experienced significant growth in treatment of both primary and metastatic disease over the past decade. Initial studies included primarily retrospective or prospective phase 2 trials for both primary HCC and colorectal metastatic disease. One of the first European observational cohort studies incorporating glass ^{90}Y microspheres into the treatment algorithm of advanced HCC demonstrated a good safety profile with an overall survival (OS) of 16.4 months and time to progression (TTP) of 10.0 months, which was comparable to systemic therapy (Hilgard et al., 2010).

A single-center longitudinal prospective cohort of 291 patients with HCC receiving glass microspheres showed the largest benefit in OS in those with Child Pugh A liver disease, with or without portal vein thrombus (PVT) and Child Pugh B liver disease without PVT, whereas Child Pugh B patients with either PVT or extrahepatic disease had significantly worse outcomes (Salem et al., 2010). Similar observations were seen in a European prospective phase 2 trial of 52 patients where a trend in OS favored those without PVT and with Child Pugh A liver disease (Mazzaferro et al., 2013).

A multicenter study evaluating prognostic factors for survival after ^{90}Y with resin microspheres in 325 patients with HCC expectedly showed the best OS in those with lower disease stages (BCLC A), whereas performance status, tumor burden, international normalized ratio levels, and presence of extrahepatic disease were the most significant prognostic variables for survival (Sangro et al., 2011). ^{90}Y has been shown to have improved OS and longer event-free survival compared to TACE in patients with HCC with stage T3 disease when attempting to downstage them to T2 disease (Lewandowski et al., 2009). This finding was replicated in a randomized phase 2 study comparing conventional TACE versus ^{90}Y in patients with BCLC stage A or B disease, showing that those treated with ^{90}Y had significantly lower TTP and less adverse events than those with TACE (Salem et al., 2016).

An early single-center retrospective propensity-matched cohort study of intermediate to advanced stage HCC comparing resin ^{90}Y to systemic sorafenib showed similar median OS between both groups but with two patients in the ^{90}Y group successfully downstaged to transplant (Gramenzi et al., 2015). Recent multicenter randomized control trials comparing resin ^{90}Y vs sorafenib were performed in both European and Asian populations. The SARAH trial consisting of 25 European centers did not show an increase in survival with ^{90}Y over sorafenib (Vilgrain et al., 2017). The similar SIRveNIB trial in Asia also did not show survival benefit with ^{90}Y compared with sorafenib but had a better toxicity profile with fewer adverse events (Chow et al., 2018). Noteworthy in both were performed with

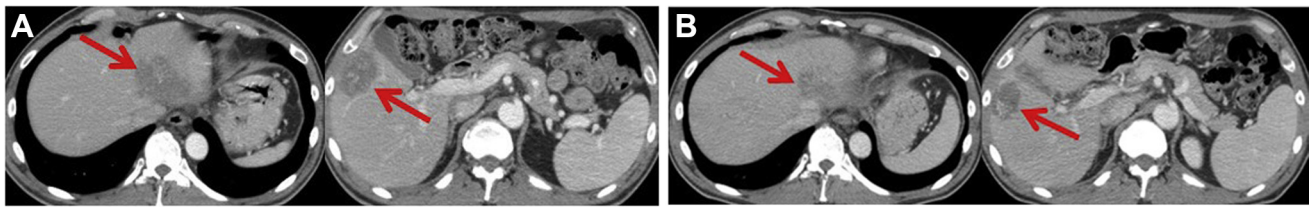

Figure 2. Patient with metastatic colorectal cancer—Pretreatment CT (A). Axial contrast-enhanced CT images through the level of the liver demonstrate two large lesions involving the right and left lobes of the liver (red arrows). Posttreatment images (B): Axial contrast-enhanced CT images through the level of the liver demonstrate significant decrease in the size of the two large lesions involving the right and left lobes of the liver (red arrows).

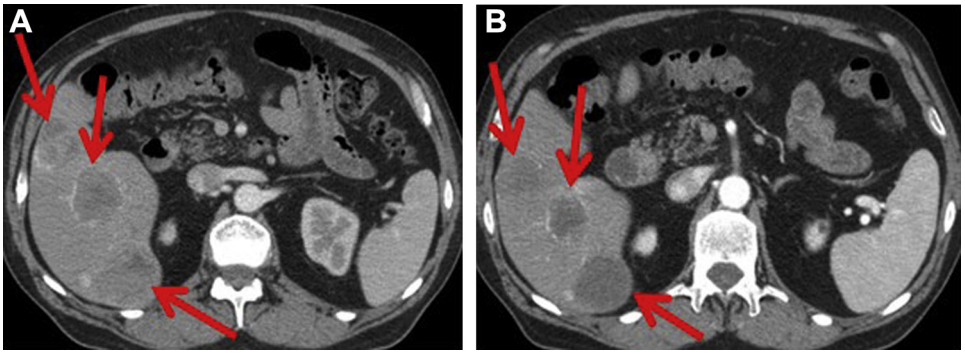

Figure 3. Patient with neuroendocrine tumor and carcinoid syndrome. Pretreatment (A): Patient with low-grade metastatic neuroendocrine tumor and refractory carcinoid syndrome. Contrast-enhanced CT scan demonstrates numerous hypervascular metastatic lesions in the right liver (red arrows). Posttreatment (B): Patient with low-grade metastatic neuroendocrine tumor and refractory carcinoid syndrome—6 months after treatment. Contrast-enhanced CT scan demonstrates the metastatic lesions in the right liver (red arrows) have decreased in size and vascularity compared with pretreatment images.

intention-to-treat analysis with 22% and 28.6% of patients in the ^{90}Y groups not actually receiving the intended radioembolization treatment in the SARAH and SIRveNIB trials, respectively. Future studies looking at the use of glass ^{90}Y microspheres versus sorafenib with unresectable HCC (STOP-HCC) are ongoing (Chauhan et al., 2018).

A more recent development has been showing the efficacy of performing ^{90}Y in a more selective fashion delivering a high-radiation ablative dose to tumor rather than the traditional lobar infusion, termed radiation segmentectomy (RS). An early study describing RS reported the ability to deliver a mean segmental dose of 521 Gy resulting in median survival of 26.9 months, with grade 3 and 4 biochemical toxicities only in 9% of patients (Riaz et al., 2011). A later study examining RS for HCC lesions less than 5 cm not amenable to percutaneous ablation showed an impressive median TTP and OS of 33.1 and 53.4 months, respectively (Vouche et al., 2014). A single retrospective study of 101 patients undergoing RS versus 103 patients undergoing TACE in a similar selective or segmental fashion demonstrated better index and overall response rates along with longer median progression-free survival with RS (Padia et al., 2017b). With promising outcomes similar to those of other curative-intent therapies, RS will likely find an increased role in those with smaller tumor burdens not eligible for ablation or resection (Lewandowski et al., 2018).

In regard to metastatic colorectal metastases, ^{90}Y has shown to have a significant survival benefit in patients refractive to chemotherapy compared with best supportive care (8.3 versus 3.5 months) (Seidensticker et al., 2012). The use of ^{90}Y has been more extensively studied in conjunction with systemic chemotherapy in metastatic colorectal liver metastases. One of the earlier phase III trials comparing systemic fluorouracil infusion alone or with resin ^{90}Y radioembolization showed that ^{90}Y significantly improved both time to liver progression and time to progression (TTP) (Hendlisz et al., 2010). The SIRFLOX study was a randomized multicenter trial looking at the benefit of adding resin ^{90}Y to first-line FOLFOX chemotherapy in patients with metastatic colorectal liver metastases. Although the addition of ^{90}Y had a longer progression-free survival and objective response rate in the liver, there was no difference in progression-free survival at any site (van Hazel et al., 2016).

More recently, the data from the combined FOXFIRE, SIRFLOX, and FOXFIRE Global randomized control trials did not show an improvement in survival with the addition of resin ^{90}Y to standard first-line chemotherapy (Wasan et al., 2017). However, subgroup analysis of data from the SIRFLOX and FOXFIRE Global trials looking at location of the primary colorectal tumors showed that patients with liver metastases from right-sided colon primaries had a significantly improved OS with ^{90}Y, whereas those with left-sided tumors did not (Gibbs et al., 2018). Therefore, the primary location and tumor biology will likely play a key role in determining the use of ^{90}Y in patients with colorectal liver metastases. Examining the efficacy of glass ^{90}Y microspheres in the context of colorectal metastases after failed first-line chemotherapy is ongoing in the EPOCH trial (https://clinicaltrials.gov/ct2/show/NCT01483027).

Although confined to retrospective or cohort studies, the use of ^{90}Y for liver metastases from other primaries has shown promise. ^{90}Y has been shown to confer an excellent disease control rate of 93% in a prospective multicenter phase II trial in patients with neuroendocrine liver metastases (Benson et al., 2013). A more recent study showed good efficacy and tolerability in this patient group, with a median survival of 29.2 months and the best radiographic responses seen in those with islet cell subtypes and hepatic tumor burden greater than 33% (Fan et al., 2016). In regard to liver metastases from breast cancer, there is evidence from retrospective studies showing efficacy in chemoresistant lesions with OS up to 13.6 months (Gordon et al., 2016; Saxena et al., 2014).

Potential complications

There are several complications that the patient and provider must be aware of with ^{90}Y infusion. The most common complications of radioembolization include nontarget radiation causing GI ulceration and pancreatitis, radiation pneumonitis, and RILD (radiation hepatitis). A mild postembolic syndrome is a common clinical toxicity characterized as fatigue, vague abdominal discomfort, pain, and fever. The incidence of nontarget radiation should be minimized with proper technique. Aggressive prophylactic embolization of collateral vessels under fluoroscopy is recommended because ^{90}Y-induced ulcers may be refractory to medical therapy in nontarget radioembolization. Proper lung shunting studies should be performed using ^{99m} Tc MAA before treatment to evaluate the risk of nontarget radiation pneumonitis. The risk of radiation-induced lung injury is mitigated if cumulative lung dose is limited to 50 Gy. Less common complications include lymphopenia, biliary injury, hepatic fibrosis, and portal hypertension, radiation cholecystitis, and idiosyncratic reactions (Ibrahim et al., 2008; Salem and Thurston, 2006).

Conclusion

Future potential applications of ^{90}Y include RS for patients with early HCC with preserved liver function who cannot undergo liver resection or ablation. Promising early results show that RS provides good response rates, tumor control, and survival outcomes

(Lewandowski et al., 2018). ^{90}Y therapy has the capability of delivering a higher dose of radiation to a small target volume with a low toxicity profile. Randomized control trials are needed to compare outcomes in patients receiving ^{90}Y versus TACE. Overall, ^{90}Y radioembolization is a safe and effective therapy for the treatment of unresectable primary and secondary hepatic malignancies.

Case 1: Hepatocellular Carcinoma

A 63-year-old male was referred to the interventional radiology clinic after discovery of a 3.3 cm mass in the liver segment 4b with imaging characteristics consistent with hepatocellular carcinoma, which did not respond to TACE performed 2 months prior (Figure 1). He had a history of well-compensated cirrhosis (Child Pugh A5) that was attributed to congestive hepatopathy from a long standing history of heart failure, for which he received a heart transplant 8 years prior. He had declined consideration of a liver transplant. He had no vascular invasion or extrahepatic disease with good performance status (ECOG 0). Given the nonresponse to TACE and preserved liver function, the decision was made to perform selective radioembolization with ^{90}Y. Figure 1 demonstrates a catheter angiogram of the middle hepatic artery showing supply to the tumor and a portion of the left hepatic lobe. This was treated with ^{90}Y glass microspheres (TheraSpheres, BTG). A follow-up magnetic resonance imaging (MR) 4 months later shows complete response without viable tumor. The patient tolerated the procedure well without liver decompensation.

Case 2: Metastatic Colorectal Cancer

The patient is a 54-year-old male with metastatic adenocarcinoma of the rectum. He underwent a left colon resection after neoadjuvant chemoradiation. The patient was diagnosed with metastatic disease to the liver and was started on systemic chemotherapy. By July of 2015, he was noted to have progression of his metastatic liver disease on chemotherapy and the patient was referred for radioembolization. At the time of referral, the patient had two metastatic liver lesions, the first was in the right lobe measuring 5.1 cm in longest dimension and the second was in the left lobe measuring 6.5 cm in longest dimension (Figure 2a). Both lesions were treated with radioembolization (SIR-Spheres), and on follow-up imaging in November of that year, the lesions had decreased in size, measuring 4.0 cm and 4.1 cm in longest dimension, respectively (Figure 2b). No new metastatic lesions were noted and the liver lesions were stable for several months.

Case 3: Neuroendocrine—Carcinoid Syndrome

The patient is a 54-year-old male with metastatic low-grade neuroendocrine tumor from a small bowel primary. The tumor was controlled with systemic oral chemotherapy and sandostatin for several years, but the patient began to complain of increased symptoms of carcinoid syndrome, specifically several episodes of flushing a day and frequent diarrhea. Given that he was demonstrating refractory syndrome symptoms with stable tumor volume, the patient was referred for radioembolization. At the time of treatment, the patient had several hypervascular tumor metastatic lesions in the right liver (Figure 3a), which had been stable for several years. During the patients posttreatment clinic visit, he described a significant reduction in his symptoms with an episode of flushing every other day and no diarrhea. Follow-up imaging performed demonstrated the treated lesions were decreased in size and significantly less vascular than the pretreatment appearance (Figure 3b).

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