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Red Flags, Pitfalls, and Cautions in Y90 Radiotherapy

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Radioembolization with yttrium-90 (Y90) microspheres is increasingly used to palliate patients with liver-dominant malignancy. With appropriate patient selection, this outpatient treatment is efficacious with limited toxicity profile. This article reviews common scenarios that can present in daily practice including evaluation of liver functions, evaluation of previous therapies, integrating Y90 into ongoing systemic therapy, determining performance status, and considering retreatment for patients who have already undergone Y90 who have hepatic dominant progression. Finally, we address the importance of evaluating tumors in potential watershed zones to maximize treatment response by using c-arm computed tomography. Many of these potential variables can overlap in an individual patient. By considering these factors individually, the consulting Interventional Radiologist can present a thorough treatment plan with a full description of expected outcomes and toxicities to clinic patients.

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Yttrium-90 (Y90) radioembolization has gained considerable interest for treatment of both primary and secondary hepatic tumors. The goal has been to decrease disease burden to allow resection or transplantation and, in patients with advanced disease, to maximize survival. Y90 therapy is well tolerated and has a favorable toxicity profile among appropriately selected patients.[1] Compared to chemoembolization, Y90 patients experience less pain and nausea. Fatigue is common following treatment and can last up to 2 weeks. However, overall quality of life is maintained at a higher level with Y90 than with chemoembolization.[2] Significant complications, such as gastrointestinal ulceration and radiation-induced liver disease (RILD), are rare. Careful patient selection can avoid these adverse outcomes. The purpose of this review is to outline our approach to patient selection and to review areas of concern that arise when considering Y90 as a treatment option.

Baseline Hepatic Dysfunction

Physicians need to proceed with caution when considering Y90 therapy in patients with poor hepatic synthetic function.[3,4] Total bilirubin is the most commonly described measure of liver function. Using chemoembolization as a historical standard, concern should increase when treating cirrhotic patients with hepatocellular carcinoma (HCC) and a bilirubin greater than 2 mg/dL. The bilirubin needs to be considered in combination with the target treatment zone within the liver. In patients requiring bilobar treatment, lesser elevations of total serum bilirubin should elevate concerns regarding the potential for fulminant liver failure with radioembolization. We are hesitant to initiate bilobar therapy in noncirrhotics with a bilirubin greater than 1.4 mg/dL (Fig. 1). We will, however, treat patients with moderate hepatic dysfunction if segmental therapy is appropriate. Sudden changes from a chronic stable total bilirubin may

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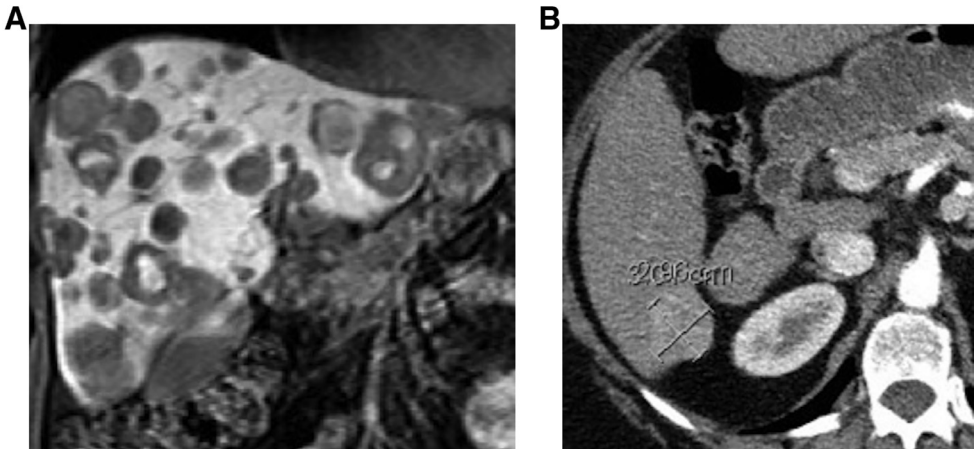

Figure 1 In a patient requiring bilobar therapy (A), a baseline total bilirubin greater than 1.4 mg/dL should be approached with caution when considering Y90. This concern should be increased in patients with metastatic disease where baseline hepatic dysfunction is uncommon as compared to hepatocellular carcinoma. For limited disease that can be treated superselectively (B), treatment with Y90 can be safely performed with elevated bilirubin. This patient with hepatocellular carcinoma and a total bilirubin of 2.8 mg/dL was safely treated.

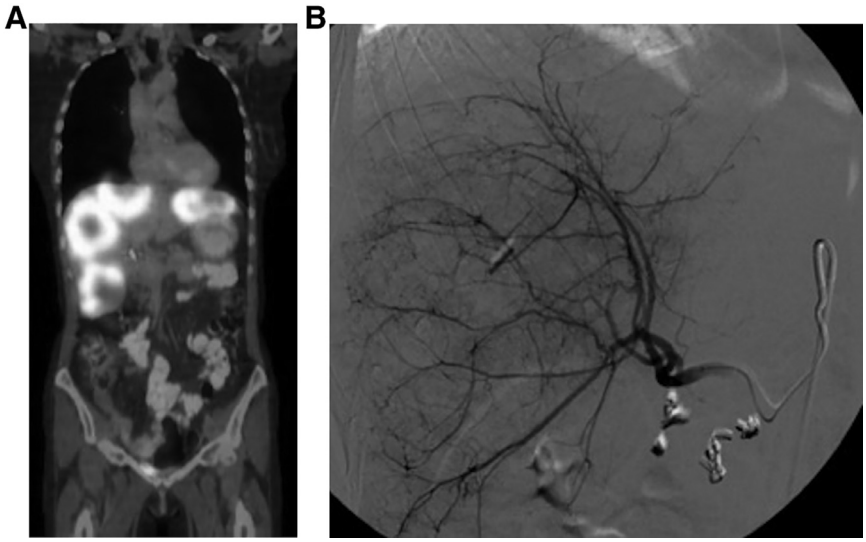

Figure 2 This 55-year-old female had metastatic colorectal cancer with chemorefractory hepatic metastases (A). After progressing on first and second line therapy, she had also been enrolled in several clinical trials. At the day of treatment (B) her total bilirubin increased to 1.6 mg/dL, which was the highest in her history. The patient was readmitted 10 days after treatment with new ascites and decreased performance status. Her imaging demonstrated no change in her tumors and maintained patency of the portal veins. She expired from hepatic decompensation a week later.

portend imminent decompensation. In this scenario, we will recheck labs in 10-14 days to assess whether this change is normal fluctuation or representing a greater danger (Fig. 2).

When evaluating hepatic function, serum albumin levels also provide valuable information as well. Albumin will frequently decrease prior to total bilirubin increase, heralding worsening of hepatic reserve and potential loss of hepatic function (Fig. 3). Brown, et al found that a serum albumin >3.4 g/dL in HCC patients undergoing chemoembolization resulted in significantly longer survival.[5] Albumin level >3 g/dL was also an independent predictor of improved survival outcomes in a cohort of metastatic colorectal cancer (CRC) patients treated with Y90 RE.[6]

Patients With an Extensive Prior Treatment History

Systemic chemotherapy can result in liver damage, even in the setting of normal serologic evaluation. Hepatic chemotoxicity and subsequent long-term outcomes remain poorly understood. Chemotherapy-associated liver injuries include sinusoidal obstruction syndrome, steatohepatitis and nodular regenerative hyperplasia (Fig. 4). Among patients with metastatic CRC undergoing liver resection following neoadjuvant irinotecan or oxaliplatin, greater than 50% had pathologically confirmed chemotherapy-associated liver injuries (grade II-III SOS, 38.4%; grade II-III steatosis 22.6%;

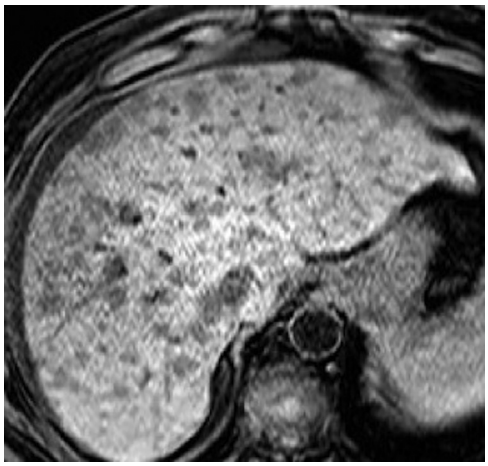

Figure 3 This patient had a history of intermediate grade metastatic neuroendocrine tumor and was referred for locoregional therapy. There is multinodular disease throughout the entire liver and anterior trace ascites (Figure). In clinic, his albumin and total bilirubin were 2.9 g/L and 1.0 mg/dL, respectively. Labs were redrawn the morning of his scheduled mapping arteriogram. His albumin had dropped to 2.4 g/L while his bilirubin was now 2.3 mg/dL. The procedure was cancelled and the patient placed on hospice. He expired 5 weeks later.

perisinusoidal fibrosis 38.1%). Notably, these patients were not heavily pretreated. Only 13.3% of patients received greater than 1 line of chemotherapy and less than 50% of patients received more than 6 cycles of chemotherapy.[7] In clinical practice, most patients referred for Y90 will have received at least 2 full lines of chemotherapy and the risk of underlying liver injury is elevated in this group. Overall survival decreases with increased previous treatments. Lewandowski et al found exposure to 2 or more lines of systemic therapy plus biologic treatment in CRC patients was an independent predictor of decreased survival.[8]

Combining Y90 With Systemic Chemotherapy

The potential benefit of combining Y90 and systemic or biologic therapy is evolving. Several drugs have been well tolerated in combination with Y90. A recent review article by Kennedy et al provides a summary of current data.[9] Based on summary review, it appears that sorafenib and irinotecan can safely be given at standard dosage with Y90. However, best practices in timing Y90 along with chemotherapy remain to be elucidated. In selected patients, we have had positive outcomes without toxicity (Figs. 5 and 6). While oxaliplatin needs to be started at a lower dose following Y90 before escalating to full dosage later in the treatment cycle, sorafenib and irinotecan appear to be safely combined with Y90 without empirical dose reduction.

There are chemotherapy agents associated with increased risk when considering Y90. Gemcitabine is a powerful radiosensitizer with significant hepatotoxicity when combined with Y90. Bevacizumab, a biologic agent that targets vascular endothelial growth factor, can induce vascular fragility increasing the risk of arterial dissection. As bevacizumab has a 20 day half-life, most operators prefer to attempt intra-arterial therapy at a minimum of 4 weeks from the most recent dose.[9] Other biologic agents reportedly also can lead to increased risk of adverse vascular events such as arterial dissection and vasoconstriction which can complicate effective microsphere delivery.[10] There is an absence of data on Y90 combined with a number of agents used in practice. Given the palliative nature of radioembolization, we recommend that practitioners err on the side of caution when considering adding Y90 to systemic, biologic or immunologic agents. Meticulous technique, thoughtful microcatheter selection, and careful wire/microcatheter manipulation are also particularly vital in this setting.

Patient Performance Status

A patient's Eastern Cooperative Oncology Group (ECOG) Score should be assessed at the initial clinic encounter and at each visit thereafter (Table). In patients with metastatic CRC, an ECOG score of 1 was associated with a significantly decreased overall survival compared to an ECOG score of 0 at multivariate analysis.[8] Patients with an ECOG score of 2 or greater have poor survival with virtually any interventional therapy and should only be treated if the procedure is expected to relieve symptoms such as severe pain or

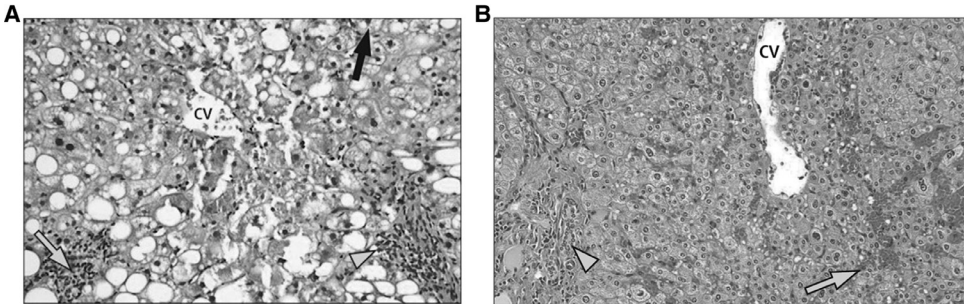

Figure 4 Changes in liver microscopy from systemic chemotherapy. (A) Steatosis secondary to irinotecan involving nearly half the liver parenchyma with degeneration of hepatocytes (arrow) as well as portal inflammation (arrowhead). CV, central vein. (B) Sinusoidal injury with congestion/dilation (arrow) following oxaliplatin (CV, central vein). Reprinted with permission: Chun YS, Laurent A, Maru D, Vauthey JN. Lancet Oncology 2009;10:278-286.

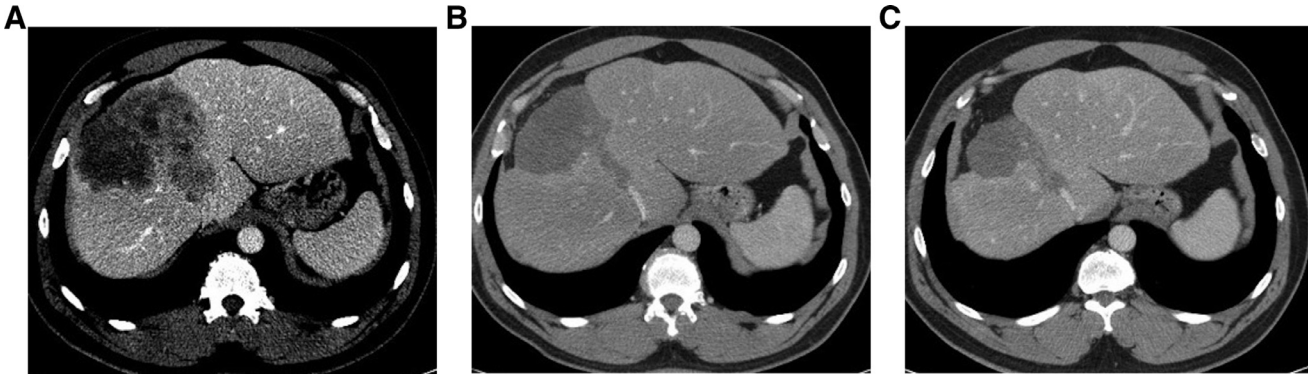

Figure 5 60-year-old male with metastatic colorectal cancer who progressed rapidly on oxaliplatin-based first line therapy. After 6 doses of irinotecan-based chemotherapy, his extrahepatic disease responded but his intrahepatic disease remained bulky including an index tumor with hepatic vein invasion (A). He was maintained on irinotecan every 14 days during treatment with Y90. We substituted Y90 for a dose of irinotecan to avoid treating him at his nadir and irinotecan was restarted at the end of the 14 day interval. One month after Y90, his index tumor decreased in size (B) and his carcinoembryonic antigen dropped from 150 to 43 ng/mL. Three months later (C), following completion of his chemotherapy, the mass continued to decrease in size and his carcinoembryonic antigen had dropped further to 20 ng/mL.

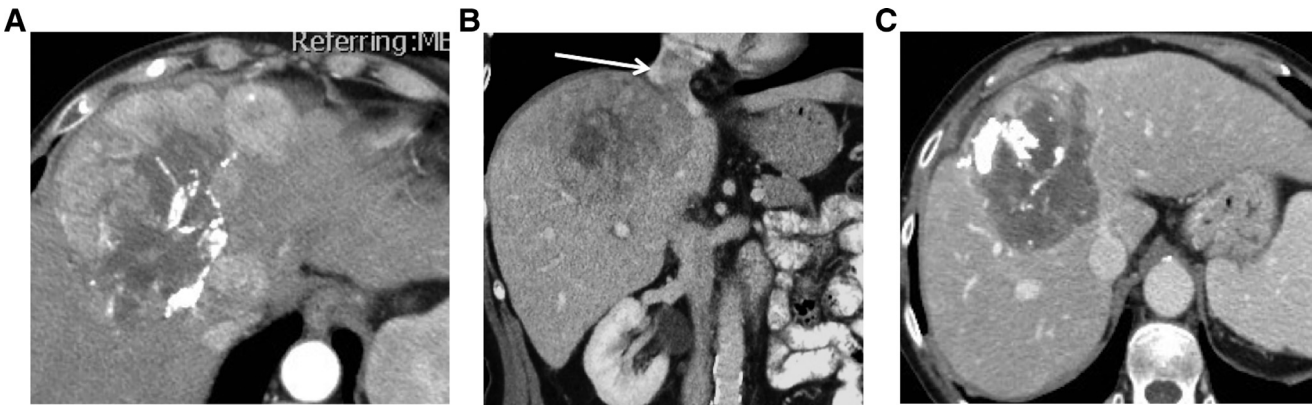

Figure 6 This 72-year-old female was diagnosed with hepatocellular carcinoma with hepatic vein invasion. She was initially treated with chemoembolization (A) which resulted in stable disease without significant change at imaging. Sorafenib was added by her medical oncologist and we planned on treating with Y90. The hepatic vein thrombus is best identified in the coronal plane (Arrow, B). She tolerated sorafenib at 200 mg twice daily which is half the full dose. We did not stop the drug for her treatment. After adding Y90 to the sorafenib, there was nearly complete tumor necrosis (C).

hormonal symptoms related to paraneoplastic syndromes. In patients with HCC there can be overlap between cancer symptoms and those from cirrhosis. The cause of symptoms is most easily discerned in patients with limited disease burden, particularly in the absence of vascular invasion or capsular distention. However, with bulky tumor and portal vein thrombosis, operators again should err on the side of caution when evaluating performance status to ensure that a patient can be safely treated.

Patients With Variant Anatomy and Other Vascular Issues

Goals of pretreatment angiography include defining target arterial supply, identification, and embolization of vessels that may lead to nontarget embolization, and determination

Table Eastern Cooperative Oncology Group Scoring System for Oncology Patients

Grade	ECOG Status
0	Fully active, able to carry on all predisease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, office work, light house work
2	Ambulatory and capable of all self-care but unable to carry out any work activities: up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

of lung shunt fraction. Variant anatomy can usually be identified on preprocedure cross-sectional imaging. In the setting of bulky, multifocal disease, lobar therapy is often the most appropriate treatment approach. For solitary tumors in the periphery of the liver, segmental or distal targeting with confirmation of coverage by c-arm computed tomography is typically performed in our practice. Central tumors, particularly those in segments 4, 5, and 8 can have dual supply from segmental branches from the left and right arteries. Careful evaluation is crucial to success. Kothary et al demonstrated a 55% complete response rate in the watershed region compared to 72% in other zones of the liver when performing chemoembolization on HCC.[11] Similarly, partially replaced segmental hepatic arteries can maintain a dual supply as well (Fig. 7). As nearly 40% of the population has some variant anatomy,[12] this issue can be commonly encountered.

Gastrointestinal ulceration is one of the most dreaded complications of Y90 radiotherapy.[13] Decision to prophylactically embolize extra-hepatic vessels such as the gastroduodenal or right gastric arteries can be safely performed with low rates of recanalization or collateral development.[14] However, there is increasing evidence that routine embolization is not required with either glass[15] or resin[16] microspheres. In our practice, this decision is based on the likelihood of reflux during arterial infusion with nearby vessels at risk. In our current practice, we embolize nontarget branches in less than 5% of patients with the greatest amount of focus on the origin of the right gastric artery in patients undergoing lobar therapy. The right gastric artery not uncommonly arises from the proximal left hepatic artery as demonstrated in Figure 8.

Portal vein thrombosis is commonly present in patients with HCC. While chemoembolization can be performed in this population, patients with lobar or more central vein invasion need to be treated by multiple segmental therapies. Y90 is a safe alternative in these patients. While treatment is feasible, we discuss outcome expectations frankly with patients in clinic. Specifically, patients with lobar portal vein thrombosis have a median survival of approximately 11 months, which is 3 times longer than those with main portal vein occlusion.[17] Additionally, patients with Child-Pugh A cirrhosis survive longer than those with Child-Pugh B or C disease.[18]

Patients Presenting for Y90 Retreatment

While Y90 can be used as a bridge to transplantation or resection, most treatments with Y90 are palliative with progressive disease an inevitable occurrence. When progressive disease remains liver dominant, repeat locoregional therapy may be a reasonable option. If repeat Y90 is considered, the cumulative effects of radiation to the lungs and liver must both be considered as excessive exposure to either of these organs can result in radiation pneumonitis/fibrosis or RILD. Y90 lung exposure from a single infusion should remain less than 30 Gy to avoid toxicity. There is evidence that this does not represent a lifetime limit.[19] Salem et al reviewed 53

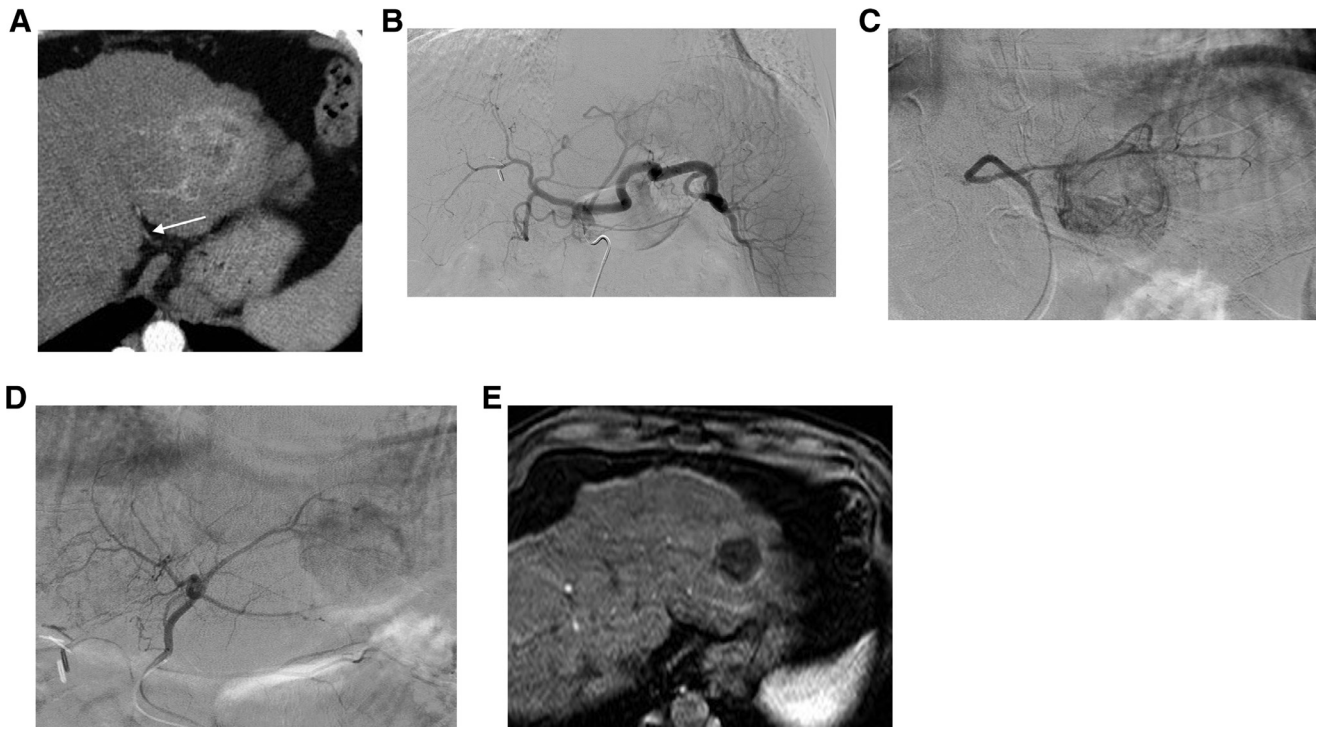

Figure 7 48-year-old with hepatocellular carcinoma in the left lateral segment (A) with a clear left hepatic artery branch traveling in the fissure of ligamentum venosum (Arrow). At celiac angiography (B), both the replaced left artery branch and a conventional left lateral segment were identified. Selection of the left lateral segmental branch (C) and the conventional branch (D), both demonstrated tumor enhancement and both were treated. At follow-up imaging (E), there was complete tumor necrosis.

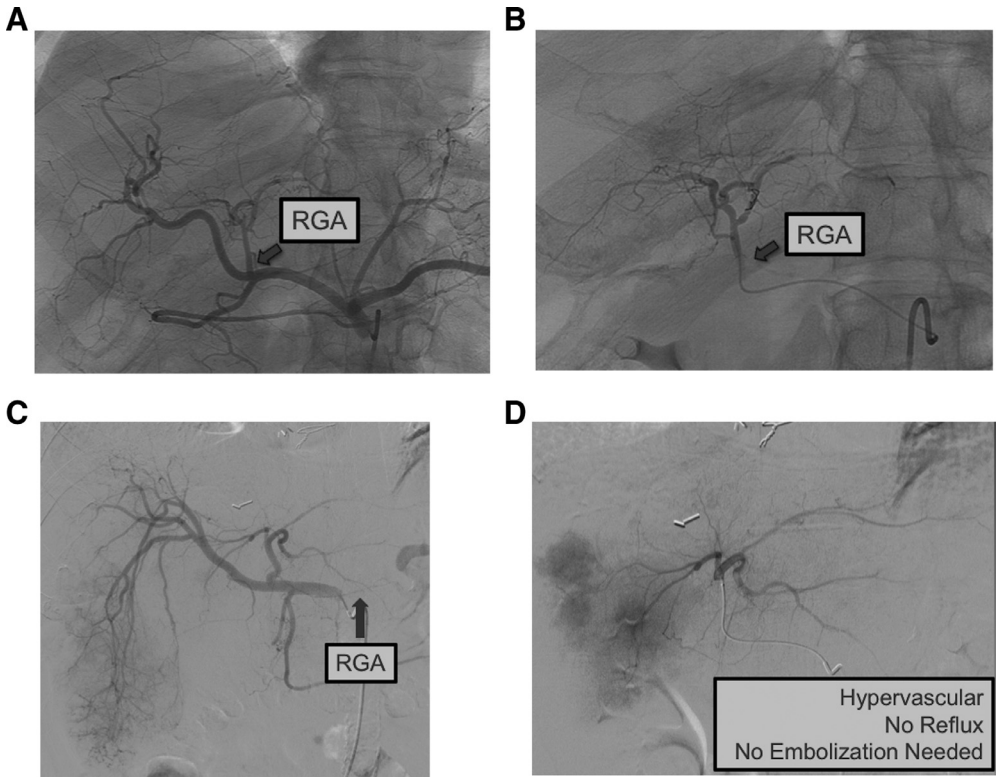

Figure 8 Selecting patients for prophylactic right gastric artery embolization. (A) At mapping angiography, the right gastric artery is identified arising from the proximal left hepatic artery (arrow). Despite selecting distal to the right gastric artery (B), there is almost immediate reflux into the right gastric branch despite power injection at a rate of only 1 cc/second. Right gastric artery embolization was performed. In another patient (C), common hepatic artery angiography demonstrates the right gastric artery similarly arising from the proximal left hepatic artery (arrow). After selecting distal to the right gastric artery branch, no reflux was identified despite power injected at 4 cc/sec. We determined that empirical embolization was not necessary.

patients who received more than 30 Gy from Y90 infusions. In patients with repeat pulmonary imaging, 43 (81%) had no imaging findings suggesting pneumonitis or fibrosis. Although the remaining patients had imaging changes associated with toxicity including pleural effusions, atelectasis and ground glass attenuation, no patients had respiratory symptoms on physical examination.

RILD is uncommon with a first cycle of therapy. In a review of 515 patients, Kennedy et al[20] described RILD in 4% of procedures. Of these patients, 75% were treated using the empirical dosimetry method and single session whole liver therapy. In current practice, the empirical dosimetry method has been virtually abandoned. Patients receiving whole liver, single session therapy, patients who were heavily pretreated with chemotherapy and those with relatively lower tumor burdens were the most likely to develop RILD.

A second session of Y90 in a previously radioembolized lobe is usually well tolerated if the contralateral lobe is disease free. In Okuda 1 HCC patients with normal liver function and prior unilobar treatment, repeat Y90 to the same lobe was well tolerated with a mean of 247 Gy (88-482 Gy). No toxicities were identified when less than 300 Gy was infused.[21] However, in Okuda 2 HCC patients undergoing repeat treatment, both mean (182 Gy) and maximal tolerated activity (361 Gy) were less than in the better-preserved cohort. Overall, repeat treatment of unilobar disease does appear to be relatively safe.

There is scant data regarding repeat treatment to both lobes of the liver. In one report, two of eight treated patients died of suspected RILD following single session, whole liver therapy when Y90 was repeated.[22] Our preference is to alternate therapies in patients with liver-dominant progressive disease following Y90. For example, we will retreat patients with neuroendocrine tumors with bland embolization or chemoembolization following previous bilobar Y90. In the setting of colorectal carcinoma with recurrent disease in the liver, we often consider use of irinotecan-eluting microspheres. If we do eventually treat with a second session of Y90, we treat in a lobar fashion with 6-8 weeks between treatments to carefully assess for hepatic decompensation.

Conclusion

In summary, Y90 is a safe treatment in appropriately selected patients. Special considerations are needed for patients with abnormal liver functions, previous polychemotherapy, diminished performance status, at risk vessels to the gastrointestinal tract, isolated watershed zone tumors, and when considering retreatment. Over the next several years, hopefully more studies

will report outcomes combining Y90 and systemic agents to improve understanding of interactions and to further integrate interventional oncology into systemic treatment algorithms.

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