Recognizing and Managing Adverse Events in Y-90 Radioembolization

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Abstract

Transarterial radioembolization using yttrium-90 (Y-90) microspheres is an important therapy in the management of unresectable primary liver tumors or hepatic metastases. While radioembolization is generally well-tolerated, it is not free from adverse events, and familiarity with the prevention and treatment of radioembolization-specific complications is an important component of patient care. This article aims to review radioembolization-specific toxicities stratified by hepatic, extrahepatic, and systemic effects, with a focus on preventing and mitigating radioembolization-induced morbidity.

Keywords

- radioembolization
- Y-90
- toxicity
- complications
- interventional radiology

Transarterial radioembolization involves arterial infusion of microspheres impregnated or coated with the β-emitter yttrium-90 (Y-90), enabling treatment of unresectable primary liver tumors or hepatic metastases. As primary and metastatic liver tumors are preferentially supplied by hepatic arterial vasculature, radioembolization delivers targeted radiation to liver tumors with lower doses to normal liver parenchyma. Given this targeted distribution, its microembolic nature, and its mechanism of action, radioembolization may be better tolerated than other treatment modalities for primary liver tumors or metastatic disease. Multiple studies have shown that radioembolization reduces incidence of grade 3 or higher adverse events (AEs), causes less postprocedure abdominal pain, decreases the frequency of postembolization transaminitis, and reduces postprocedure lengths of stay relative to transarterial chemoembolization and systemic therapies.[1–3] Others have found that radioembolization significantly improves components of quality of life relative to patients undergoing chemoembolization.[4]

Despite being generally well-tolerated, radioembolization is free of neither morbidity nor mortality, and contemporary prospective studies report a serious AE rates (grade 3 or higher) of 2.5%, with 30-day all-cause mortality rates of 1.0%.[5] Such toxicities may vary according to patient population and microsphere type used, but are generally mediated through radiation of normal hepatic parenchyma, nontarget embolization, and systemic elution. As radioembolization becomes an increasingly common tool in the treatment of primary and secondary liver tumors, a familiarity with the prevention and treatment of commonly encountered toxicities is key. This review aims to provide a review of morbidity in radioembolization stratified by local, extrahepatic, and systemic effects as well as by microsphere type, with a specific focus on mitigating morbidity and reviewing management of radioembolization-induced toxicities.

Local Effects

Radioembolization-Induced Liver Disease

As a result of radiation-induced microscopic obliteration of hepatic veins, hepatic congestion, and secondary hepatocyte necrosis, radioembolization-induced liver disease (REILD) may develop acutely to subacutely after radioembolization.[5] REILD results in liver function derangement, elevated bilirubin and LFTs, and ascites within 4 to 8 weeks following radioembolization in the absence of other explanations such as tumor progression or biliary duct obstruction.[5] The incidence of REILD is difficult to quantify due to differences in patient characteristics, time to follow up, and toxicity definitions in the literature. However, large retrospective and prospective studies suggest a rate of 1.0 to 5.4%.[6,7] REILD incidence increases in patients with underlying liver dysfunction or

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cirrhosis, and similarly increases in patients with decreased hepatic reserve, such as those with diffuse hepatic metastases or small functional liver volumes.[5,8] Literature assessing the role of systemic chemotherapy in potentiating radioembolization liver toxicity is mixed, but studies suggest that several chemotherapeutic agents, including 5-FU, capecitabine, oxaliplatin, and irinotecan, interact synergistically with radioembolization and increase parenchymal radiosensitivity, increasing risk of REILD.[7,9] The effect of increased cumulative radiation exposure in REILD remains unclear, with both prospective and retrospective studies showing similar to moderately increased risk of REILD with multiple treatments to the same vascular distribution.[10–12]

Challenges arise in assessing long-term toxicity of radioembolization because of the many confounding therapies patients with progressive malignant disease are offered. However, in single-center studies, 21 to 56% of noncirrhotic patients with metastatic disease are reported to develop cirrhosis-like liver morphology and stigmata of portal hypertension after radioembolization.[10,11] These changes were more frequently encountered in patients treated with whole-liver radioembolization compared with those with therapy limited to one lobe. Fortunately, significant clinical manifestations of these morphologic changes are uncommon. In one single-center retrospective study, chronic hepatotoxicity (defined as permanent grade 3 or higher clinical or functional hepatoxicity at least 6 months after radioembolization) was reported in at most 13% of patients surviving more than 1 year after radioembolization.[13] In addition to whole-liver radioembolization, treatment of tumors involving more than 50% of liver volume and underlying cirrhosis predict incidence of chronic hepatotoxicity, though attribution of long-term toxicity to individual causative factors is challenging due to confounding effects of other systemic and locoregional therapies in addition to the malignancy itself.[13]

Prophylactic strategies to prevent REILD and chronic hepatotoxicity are limited. Observational, single-arm studies suggest that a 2-month course of ursodeoxycholic acid and methylprednisolone taper beginning on the day of radioembolization may prevent REILD.[5] This strategy, adapted from randomized controlled trials demonstrating efficacy in reducing whole-body radiation-induced liver disease in bone marrow transplant patients, lacks prospective validation in patients undergoing radioembolization. Instead, REILD prevention centers on appropriate patient selection. Patients with underlying advanced liver disease, baseline elevated bilirubin levels, ascites, or Child–Pugh class C disease are at significantly increased risk of REILD, and alternatives to radioembolization should be considered.[5,8] Similarly, patients with a small volume of uninvolved liver parenchyma, such as those with diffuse hepatic disease or posttreatment patients with a small functional liver remnant, should be carefully screened for underlying abnormal background liver parenchyma. In such patients, and particularly in patients undergoing whole-liver radioembolization, a dose reduction of 10 to 20% has been shown to markedly decrease rates of REILD.[5,8] Similarly, in patients treated with systemic chemotherapy pre- or post-radioembolization, chemotherapeutic dose reduction or timing modifications can be considered.[7] Finally, by limiting the volume of normal liver parenchyma treated using selective radioembolization, REILD and other AEs can be minimized.[14]

Intrahepatic Biliary Dysfunction

Biliary AEs, such as cholangitis or biloma formation, reflect an infrequent subset of post-radioembolization complications, reported in 1.0 to 3.9% of patients.[8,15] This low complication rate is presumed due to the microembolic effect of the microspheres relative to larger particles used in bland embolization and chemoembolization, which minimizes the risk of biliary necrosis.[8] Multicenter studies have accordingly not shown a significantly increased risk of radioembolization-induced biliary injury in patients with cholangiocarcinoma or biliary obstruction. For instance, Buettner et al reported no biliary AEs in 115 cholangiocarcinoma patients treated with radioembolization.[16] Given the overall low rate of radioembolization-induced biliary injury, biliary obstruction due to cholangiocarcinoma should not be considered a contraindication to treatment, though ablative radioembolization (radiation segmentectomy) should be used with caution in patients with contaminated bile ducts due to the potential for parenchymal necrosis and consequent infection (►**Fig. 1**).[17,18]

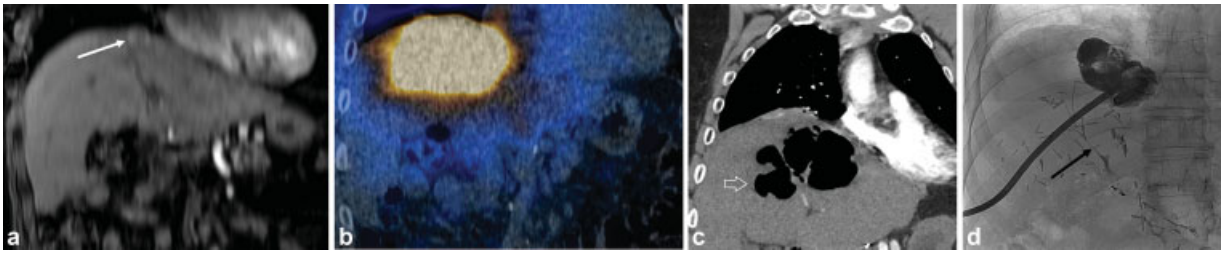

Fig. 1 Infected biloma complicating radioembolization. A 65-year-old man with recurrence following partial hepatectomy and pancreaticoduodenetomy for metastatic pancreatic neuroendocrine tumor. Contrast-enhanced coronal MR image demonstrates a segment 4 metastatic tumor (white arrow) (**a**). The lesion was treated with ablative-dose segmental radioembolization (radiation segmentectomy); posttreatment bremsstrahlung-fused coronal SPECT/CT image reveals deposition of the Y-90 microspheres in the target segment (tan) (**b**). Despite a 3-week course of prophylactic oral antibiotics, the patient returned with fevers and pain 3 months after treatment. Coronal image from CT chest shows a large intrahepatic abscess (arrow = gas in the abscess cavity) (**c**). This was treated with antibiotics and percutaneous drainage. At a subsequent drain revision, injection of the abscess catheter reveals communication with the bile ducts (black arrow) (**d**). Ultimately, the infected biloma resolved, the drain was removed, and the metastatic tumor showed complete response.

Prophylactic antibiotics, which reduce the risk of bilomas or hepatic abscesses in bland embolization and chemoembolization, may be used to similar effect in radioembolization, though prospective evidence of efficacy is limited.[8,19]

Local Radiation to Adjacent Structures

While radioembolization presents a theoretical risk of extrahepatic radiation injury, Y-90 β-radiation tissue penetration is low, with mean and maximum path lengths of 2.5 and 10 mm, respectively.[20] Prospective data on extrahepatic injury due to tissue penetration from the treated lesion are limited, but there is little evidence that this mechanism contributes to post-radioembolization toxicity. For instance, in a retrospective study evaluating effects of Y-90 radioembolization of left hepatic tumors within 1 cm of the stomach, 42% of patients reported self-limited grade 1–2 abdominal pain, but no gastrointestinal (GI) ulceration was reported, and GI ulceration is more commonly encountered due to nontarget embolization rather than adjacent parenchymal radiation.[21] Irradiation of perihepatic soft tissues may result in adhesions between the liver, diaphragm, or bowel, but this is rarely of any significance unless the patient undergoes resection, which may offer a challenge to some surgeons.[22,23]

Nontarget Distribution

Radiation-Induced Lung Disease

Radiation pneumonitis or radiation-induced lung disease is characterized by development of dry cough, fever, and radiographic ground-glass attenuation or consolidation on chest CT following lung exposure (►**Fig. 2**). Acute symptoms present within 3 to 12 weeks of treatment, and while they may be self-limited, chronic fibrosis can develop within as little as 6 months.[24] Radiation-induced lung disease has been well-characterized in the radiation oncology literature, with risk factors during EBRT including the volume of irradiated lung receiving a dose greater than 20 to 30 Gy.[25,26] Due to neoangiogenesis and intrahepatic arteriovenous shunting within hepatocellular carcinoma (HCC) and hepatic metastases, radioembolization poses a risk of nontarget pulmonary exposure, as the Y-90 microspheres escape to the lungs through the abnormal tumor neovascularity. As such, dose limitations have been extrapolated from the EBRT literature and applied to radioembolization, with 30 and 50 Gy now set as the per-treatment and cumulative dose limits, respectively, for both glass and resin microspheres.[26] These numbers have superseded original recommendations to reduce Y-90 dose in patients with lung shunt fractions (LSF) greater than 10%, and to defer treatment in patients with LSF greater than 20%, aided by studies reporting no cases of radiation-induced lung disease in a cohort of high-LSF (>15%) patients treated with single-session doses of less than 30 Gy.[27]

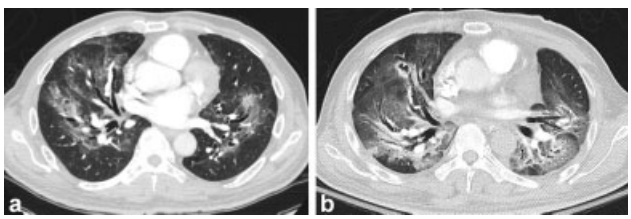

Fig. 2 Radiation pneumonitis complicating radioembolization. A 56-year-old man with chronic hepatitis B and unresectable hepatocellular carcinoma in the right hepatic lobe with portal vein and inferior vena cava invasion was treated with hepatic radioembolization. Mapping angiography was completed, and the lung shunt fraction was estimated at 22%. He was treated with an estimated dose of 27 Gy. The patient developed dyspnea, and CT chest 4 months after treatment showed changes of "batwing" appearance of ground-glass attenuation with peripheral sparing (**a**). Despite treatment with steroids, symptoms were progressive on CT findings (**b**). The patient died shortly thereafter.

The overall incidence of radiation-induced lung disease is low, reported at less than 1% across prospective and retrospective studies.[8] Preventative measures include adherence to the recommended dose limitation of 30 Gy per treatment session, as well as careful consideration in treating patients with preexisting interstitial lung disease, which predisposes patients to increased susceptibility to further lung injury. For patients with significant hepatopulmonary shunting, several strategies may reduce lung shunt fraction and mitigate radiation-induced lung disease risk, including prophylactic transient hepatic venous balloon occlusion, or transarterial bland- or chemoembolization prior to radioembolization.[28,29] Additionally, a staged or fractionated approach to radioembolization may allow sufficient treatment of the tumor-related hepatopulmonary shunt to permit a subsequent and more definitive treatment. Finally, pre-radioembolization administration of at least 4 weeks oral sorafenib, a multikinase inhibitor with antiangiogenic properties, has also been reported to successfully reduce lung shunt fraction without interval tumor progression.[30]

Despite the low incidence of radiation-induced lung injury, providers should have a low threshold for chest radiography or CT if patients report dyspnea, cough, or chest pain after radioembolization. If ground-glass attenuation or consolidations are identified, functional testing can identify restrictive lung disease, and bronchioalveolar lavage or parenchymal biopsy can be considered to assess for alternative causes of lung disease. Management of radiation-induced lung injury is supportive, and no controlled studies have evaluated the efficacy of medical therapy in its management. However, standard treatment includes glucocorticoids, antitussive therapies, and oxygen if needed.[31]

Gastrointestinal Embolization

Nontarget GI radioembolization can occur in the setting of unidentified variant anatomy or collateral circulation, changes in flow dynamics during radioembolization, or microsphere reflux. Low doses of radiation may decrease gastric acid production and cause mucosal thinning, edema, and chronic inflammation, which manifests clinically as gastroenteritis, mucositis, or ulceration. Symptoms often present acutely to subacutely, with nausea, vomiting, anorexia, abdominal pain, and/or upper GI bleeding presenting within 2 to 3 weeks after treatment, though delayed ulceration or stenosis has been reported between 1 and 12 months

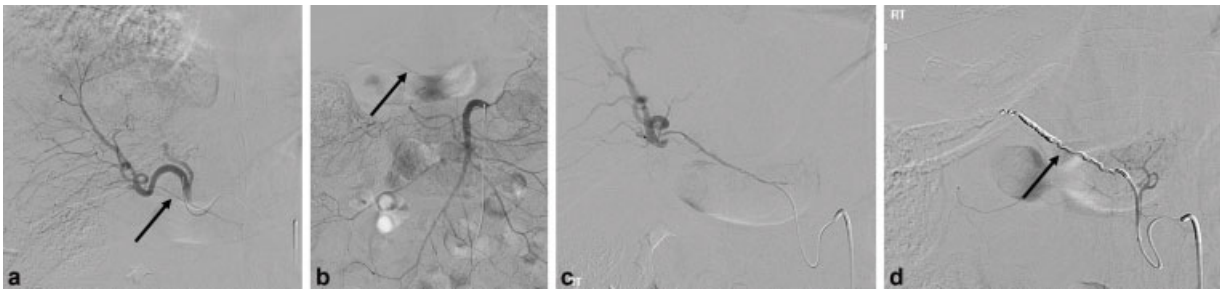

Fig. 3 Coil embolization of a retroduodenal artery. A 53-year-old woman underwent mapping angiography in anticipation of lobar radioembolization for metastatic colorectal cancer with resin microspheres. Selective right hepatic angiography demonstrated a conspicuous artery (arrow) coursing inferiorly, away from the liver (**a**). Review of the superior mesenteric arteriography revealed this same vessel (arrow), which was determined to be a retroduodenal artery (**b**). The artery could not be selected from the right hepatic artery but was easily selected from the superior mesenteric anastomosis. Injection shows retrograde filling of the right hepatic distribution (**c**). After coil embolization of the retroduodenal artery (arrow) to minimize risk of nontarget radioembolization (**d**), the patient was safely treated.

after treatment.[32] The published incidence of symptomatic nontarget GI embolization varies widely and has decreased as radioembolization techniques have evolved, though it is estimated at 1.9 to 3.2%, and may be lower in contemporary practice.[9,33]

Given the potential severity of this AE, prevention of nontarget GI radioembolization is critical. Prevention begins with meticulous mapping angiography. Both nonselective and selective angiography should be carefully scrutinized during mapping, and the origins of the right gastric, left gastric, or accessory left gastric and gastroduodenal arteries should be identified, as should variant anatomy such as supraduodenal and retroduodenal arteries (►**Fig. 3**).[34] If arteries at risk for GI nontarget radioembolization are identified at mapping, these may be embolized with coils; coil embolization is ideally performed prior to administration of the Tc99m-macroaggregated albumin (MAA) mapping dose, though can be performed during treatment angiography if needed.[33] Tc99m-MAA SPECT images should be closely reviewed for extrahepatic localization but should not be relied upon over high-quality angiography to exclude nontarget GI deposition. Although rarely encountered, uncorrectable nontarget GI deposition is a contraindication to radioembolization. In these cases, alternative therapies (such as systemic therapies, bland embolization, or chemoembolization) should be considered.

Proximal (such as common or proper hepatic arterial) catheter treatment positions, which had been used more often historically, are an independent predictor of nontarget GI radioembolization and should be avoided.[34] At treatment, the catheter should be positioned as closely as possible to that of the position of Tc99m-MAA infusion during mapping angiography, to ensure a similar distribution of microspheres. Microsphere reflux can be avoided via slow, consistent injection and cessation of treatment prior to stasis, as stasis also independently predicts risk of nontarget GI embolization.[34] Microsphere choice can also influence risk of reflux and nontarget embolization, as use of resin microspheres correlates with a small but increased incidence of grade 3 or higher AEs, including GI ulceration (1.4 vs. 0.1% in patients treated with glass microspheres).[35] Following treatment, Bremsstrahlung images may be reviewed to identify inadvertent nontarget embolization.

Outside of appropriate mapping and treatment technique, data on prophylaxis to prevent radiation-induced bowel injury from nontarget embolization are limited, and medication prophylaxis (such as proton-pump inhibitors) is not routinely prescribed prior to radioembolization. If prescribed empirically following radioembolization, proton pump inhibitors should be prescribed for at least 8 weeks, allowing sufficient time for mucosal recovery.[36] Upper endoscopy is recommended in a patient with persistent upper abdominal pain 2 to 8 weeks after radioembolization, as the differential diagnosis for post-radioembolization abdominal pain includes cholecystitis or pancreatitis stemming from nontarget embolization, non-iatrogenic GI ulceration (e.g., nonsteroidal anti-inflammatory drug, *Helicobacter pylori*, or stress-induced ulceration), or disease progression, among others. Upper endoscopic biopsy also permits definitive diagnosis of nontarget embolization, as microspheres lodged in capillary beds are visible on microscopy.

First-line management of symptomatic nontarget GI embolization is medical, with treatment including high-dose PPIs, sucralfate, and avoidance of nonsteroidal anti-inflammatory drugs; chemotherapy may need to be deferred to allow for healing. A majority of patients will progress to clinical/endoscopic recovery with these conservative measures. In severe cases, however, bowel rest (such as distal enteric feeding or total parenteral nutrition) may be necessary, and up to 6% of patients in large case series require surgery.[36]

Gallbladder Embolization

Nontarget gallbladder radioembolization is uncommon, resulting in radiation cholecystitis in up to 2.0% of patients, and less commonly in gallbladder ulceration or necrosis.[8,9] As with other forms of nontarget embolization, prevention is critical. The cystic artery should be identified at the time of mapping and treatment, and, if possible, treatment should be performed distal to its origin, though selective radioembolization of the cystic artery may be safe in some instances of tumor perfusion by the deep branch of the cystic artery.[37] If safe radioembolization is not otherwise feasible, the cystic

artery may be temporarily occluded using Gelfoam. However, prophylactic cystic artery coil embolization has not been shown to decrease rates of radioembolization-induced cholecystitis, and may instead predispose patients to ischemic cholecystitis.[38]

While rare, radioembolization-induced cholecystitis is generally amenable to conservative management with hydration, pain control, and antibiotics. If gallbladder ulceration or perforation is suspected, cholecystectomy should be considered. Similar to management of conventional cholecystitis, patients who are critically ill or unlikely to tolerate cholecystectomy may instead benefit from cholecystostomy tube placement.[15]

Cutaneous Embolization

Radioembolization-induced cutaneous injury may result from nontarget embolization to the falciform artery or parasitized extrahepatic arterial supply. While reported cases are usually mild, severe dermatitis or ulceration has been infrequently reported.[39] Given the generally diminutive caliber of these vessels and small cutaneous distribution, severe (grade 3 or greater) AEs from nontarget cutaneous embolization are rare. Prevention of nontarget embolization is thus desirable but not critical. Falciform artery coil embolization may be attempted (►**Fig. 4**), but benefits of embolization must be balanced with risk of hepatic arterial branch spasm or dissection during coiling.[10] Less invasive preventative strategies include placement of an ice pack over the umbilicus or tissue at risk during embolization, resulting in temporary vasoconstriction and decreased blood flow to this distribution.[40]

Systemic Effects

Postembolization Syndrome

Postembolization syndrome, a constellation of fatigue, anorexia, abdominal pain, nausea, and/or vomiting, is the most commonly reported AE following radioembolization, with abdominal pain, fever, and nausea reported in 13 to 39%, 2 to 12%, and 17 to 32% of patients undergoing radioembolization for HCC and metastatic colorectal cancer, respectively, with a total incidence of 20 to 55%.[9,15,41] This syndrome is mild and self-limited in a majority of cases, with management of symptomatic patients including both nonnarcotic and (if needed) narcotic pain medications, antiemetics, and hydration, and glucocorticoids as needed in severe cases.[41]

Lymphopenia

While systemic toxicities after radioembolization are limited due to the mechanism of Y-90 delivery, with the radionuclide either incorporated within or tightly adsorbed to glass or resin microspheres, respectively, neutropenia and lymphopenia have still been reported in patients undergoing radioembolization. Such findings may in part be due to trace systemic elution; in a prospective study, investigators found 1.0% elution of Y-90 from resin microspheres, resulting in a red marrow dose of 132.3 mGy (effective dose: 18.5 mSv).[42] While this dose is small, synergistic interactions between radioembolization and concomitant systemic chemotherapy may increase risk of marrow toxicity. For example, attempted combination therapy with radioembolization and FOLFOX in the SIRFLOX trial resulted in dose-limiting

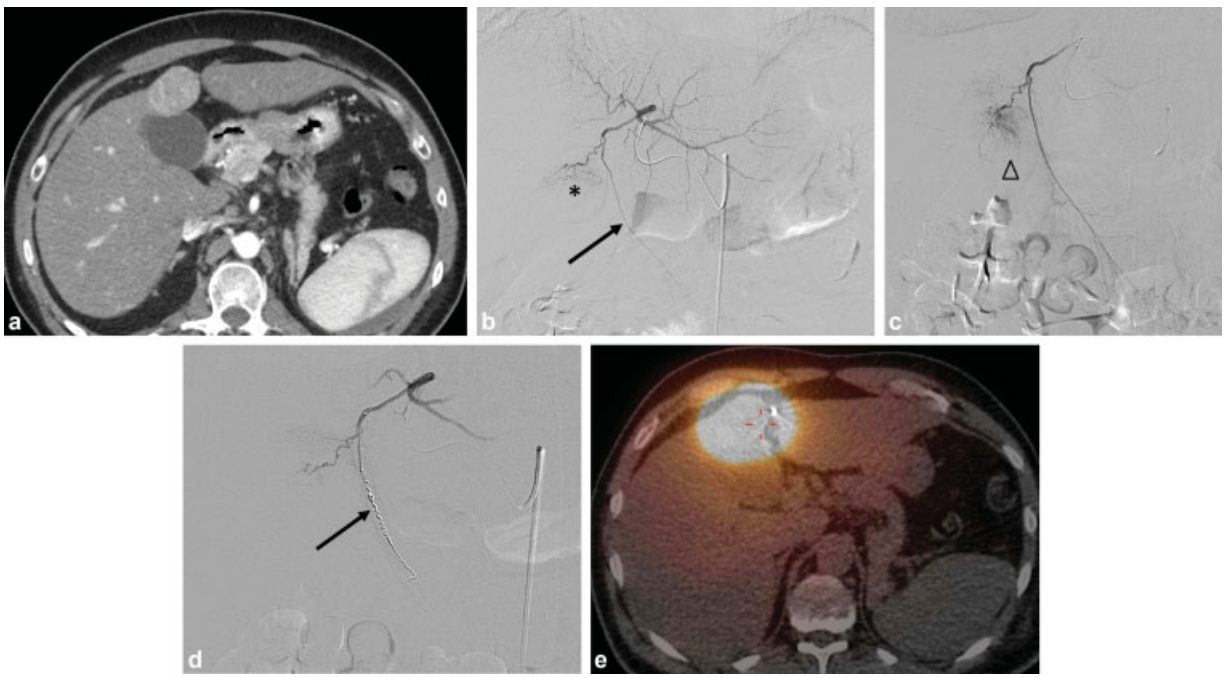

Fig. 4 Coil embolization of a falciform artery. A 64-year-old man with hepatitis C virus cirrhosis and CT presented with a 3-cm subcapsular hepatocellular carcinoma (HCC) abutting the gallbladder (**a**). With plans for Y-90 radiation segmentectomy as a bridge to liver transplant, he underwent mapping angiography. Left hepatic arteriography shows tumor vascularity (asterisk) partially supplied by the falciform artery (arrow) (**b**). Selective arteriography before (**c**) and after (**d**) coil embolization (black arrow) of the falciform artery. (Arrowhead = tumor vascularity). Bremsstrahlung SPECT/CT shows expected focal deposition of Y-90 microspheres in the HCC and no nontarget Y-90 deposition. The patient subsequently underwent liver transplant.

grade 3/4 neutropenia, leading to oxaliplatin dose reduction in patients randomized to radioembolization plus chemotherapy. Even with this modification, neutropenia and thrombocytopenia occurred significantly more frequently in patients receiving radioembolization and chemotherapy than in patients receiving chemotherapy alone, though at a manageable frequency and severity.[7]

Effects by Microsphere Type

Two devices are commercially available for use in radioembolization. Glass microspheres are 20 to 30 µm in size, with Y-90 directly incorporated into the microsphere. Resin microspheres are similar in size (20–60 µm), with surface-conjugated Y-90. Dosing differs between these microspheres, as glass microspheres deliver 2,500 Bq per microsphere, while resin microspheres deliver 50 Bq per microsphere. Taken together, these differences in physical and radiologic composition predispose to differences in delivery, with a greater number of resin microspheres needed to administer a given dose.[35]

Glass microspheres are currently approved for treatment of unresectable HCC, while resin microspheres are approved for use in patients with unresectable metastatic colorectal cancer. Aside from the lack of studies directly comparing the devices, differing practice patterns and properties between the two devices have confounded assessment of differences in adverse effect profiles. However, a recent meta-analysis of 31 observational studies assessing AE profiles of resin and glass microspheres showed differing rates of grade 3 or higher AEs between agents.[32] While glass and resin microsphere-treated patients had similar rates of postembolization syndrome, resin microsphere use correlated with slightly increased incidence of grade 3 or higher GI ulceration (1.4 vs. 0.1% in glass microsphere–treated patients), cholecystitis (5 vs. 1.9% in glass microsphere–treated patients), hepatic failure (22.2 vs. 6.9% in glass microsphere–treated patients), and hepatic encephalopathy (8 vs. 2.8% in glass microsphere–treated patients).[35] Conversely, glass microsphere use correlated with increased incidence of grade 3 or higher ascites (6.1 vs. 2.7% in resin microsphere–treated patients), pleural effusions (0.5 vs. 0.0% in resin microsphere–treated patients), and prolonged nausea (1.5 vs. 0.4% in resin microsphere–treated patients).[35]

Despite these differences, overall observed AE rates remain low across device types. Additionally, practice parameters for both glass and resin microspheres continue to evolve, including prophylactic coil embolization of territories at risk for nontarget embolization, routine inspection of Tc99m-MAA mapping SPECT/CT to assess for nontarget deposition, and technical changes in resin microsphere administration (e.g., routine use of 5% glucose rather than sterile water during resin microsphere administration). Prospective, direct comparisons of microsphere toxicities are as of yet unavailable.

Conclusions

In summary, radioembolization is a well-tolerated tool in the treatment of unresectable primary liver cancer and metastatic disease, with common side effects presenting as self-limited nausea, vomiting, anorexia, and abdominal pain. Though severe adverse effects are rare, complications such as radiation-induced liver and lung disease and nontargeted GI embolization merit close attention to appropriate patient selection, careful preprocedure planning, and close postprocedural follow-up.

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