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Yttrium-90 Radioembolization for Hepatocellular Carcinoma

Ryan M. Hickey, MD,* Robert J. Lewandowski, MD,* and Riad Salem, MD*

^{90}Y radioembolization refers to the selective, transcatheter, and intra-arterial injection of micrometer-sized particles loaded with the radioisotope yttrium-90 for the treatment of primary and metastatic hepatic malignancies. In the treatment of intermediate- and advanced-stage hepatocellular carcinoma, ^{90}Y radioembolization provides favorable outcomes with minimal side effects, offering an alternative treatment option to other transarterial therapies, such as bland embolization and chemoembolization. This review provides an overview of the use of ^{90}Y radioembolization in the treatment of hepatocellular carcinoma, including patient selection criteria, dosimetry, and clinical outcomes.
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Introduction

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death worldwide.[1] In Western countries, it most often occurs in patients with chronic liver disease due to viral hepatitis, alcohol-induced liver disease, or nonalcoholic steatohepatitis. Globally, nearly 80% of HCC cases are related to chronic hepatitis B and C infection.[2]

The Barcelona Clinic Liver Cancer (BCLC) staging and treatment system is the most widely accepted staging system used in clinical practice and trials in Europe and the Americas, and it is the recommended staging system for prognosis prediction and treatment allocation. Patients are separated based on the severity of underlying liver disease and tumor burden into very early, early, intermediate, advanced, and terminal stages. Treatment recommendations are based on the BCLC stage and include curative therapies for very early and early-stage HCC, palliative therapy for intermediate- and advanced-stage HCC, and symptomatic management for terminal-stage HCC.[3,4] More recently, the Hong Kong Liver Cancer (HKLC) staging and treatment algorithm has been validated for HCC in Asian populations.[5]

*Department of Radiology, Division of Vascular & Interventional Radiology, Northwestern University, Feinberg School of Medicine, Chicago, IL.
Address reprint requests to Riad Salem, MD, Department of Radiology, Division of Vascular & Interventional Radiology, Northwestern University, Feinberg School of Medicine, 676 N St Clair St, Suite 800, Chicago, IL 60611. E-mail: r-salem@northwestern.edu

The BCLC and HKLC algorithms allocate patients with intermediate-stage HCC (BCLC) or intermediate and locally advanced HCC (HKLC) to locoregional treatment with transarterial chemotherapy (TACE). Transarterial radioembolization with yttrium-90 (^{90}Y) microspheres is an alternative transarterial treatment option to TACE, which offers similar survival outcomes, a longer time to tumor progression (TTP), and a significantly lower toxicity profile compared with those of TACE.[6-9]

^{90}Y Radioembolization

Radioembolization refers to the selective, transcatheter, and intra-arterial injection of micrometer-sized particles loaded with ^{90}Y. The radioisotope yttrium-90 is a pure beta emitter with a half-life of 64.2 hours and tissue penetration of 2.5-11 mm that is irreversibly incorporated into glass or resin microspheres that range in size from 20-30 μm (glass) or 20-60 μm (resin). Glass microspheres (TheraSphere, BTG, London, UK) were approved in 1999 by the US Food and Drug Administration (FDA) under a humanitarian device exemption for the treatment of unresectable HCC.[10] Resin microspheres (SIR-Spheres, Sirtex Medical, Lane Cove, Australia) were granted full premarketing approval in 2002 by the US FDA for the treatment of unresectable colorectal metastases in conjunction with intrahepatic floxuridine.[11]

Microcatheters, on the order of 2-3 Fr in size (<1 mm diameter), are advanced into branches of the right and left hepatic arteries that perfuse tumor-containing liver tissue

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using angiographic guidance and technique. High tumoral radiation doses achieved with radioembolization rely on the preferential deposition of particles within tumor tissue as opposed to normal liver tissue because of differences in perfusion of normal liver and tumor tissue. Whereas normal liver parenchyma receives most of its blood supply (~75%) from the portal vein, hepatic malignancies, particularly hypervascular malignancies such as HCC, receive most of their blood supply from the hepatic arteries.[12,13] Intra-arterial injection of the radioactive microspheres results in greater deposition of the microspheres in the arterially perfused tumors compared to liver parenchyma.

Whereas the radiosensitive nature of normal liver tissue has limited the role of external-beam radiation in the treatment of primary and metastatic hepatic malignancies, radioembolization allows for safe administration of high and therapeutic doses of radiation. The likelihood of developing severe radiation-induced liver disease may exceed 50% for external-beam radiation doses greater than 35-40 Gy, whereas radiation doses greater than 150 Gy have been safely administered with radioembolization.[14-17]

Patient Selection

Eligibility for transarterial radioembolization requires assessment of the patient's burden of disease, biochemical parameters, and performance status. Patients should have liver-only disease with a tumor burden involving less than 50% of the liver. A bilirubin level ≤ 2 mg/dL, albumin > 3 g/dL, and normal international normalized ratio have been used as indicators of adequate hepatic reserve and synthetic function. Cancer-related symptoms should be minimal, corresponding to an Eastern Cooperative Oncology Group score of 0-2. Although the presence of portal vein thrombosis (PVT) has been traditionally considered a contraindication to hepatic arterial embolization procedures, radioembolization has been shown to be safe and effective in the setting of PVT.[6,18] Radioembolization should be avoided in patients who have had intervention or surgery involving the ampulla of Vater due to an increased risk of hepatic abscesses following the procedure.

Lung-Shunt Fraction

^{90}Y radioembolization is performed on an outpatient basis and involves two separate angiography procedures. An initial mapping angiography is performed, at which time a radioisotope lung shunt fraction is also determined. ^{90}Y microspheres are then administered during a separate treatment angiography.

HCC is associated with a relatively high incidence of direct arteriovenous shunts that bypass the tumor capillary bed.[19] The administration of microspheres smaller than these shunts could therefore result in direct shunting of the radioactive microspheres to the lungs, which can cause radiation pneumonitis at sufficient doses.[20]

Technetium-99m (^{99m}Tc-macroaggregated albumin [MAA]) is of similar size to the ^{90}Y microspheres and expected to mirror their distribution, including in pulmonary shunting. Between 75-150 MBq (2-4 mCi) of ^{99m}Tc-MAA is administered via the proper, right or left hepatic artery, depending on the planned treatment site, at the conclusion of the initial angiography. The patient is then transferred to nuclear medicine for acquisition of planar gamma camera images, with or without concomitant single photon emission CT (SPECT) gamma camera images, which are used to calculate the fraction of administered ^{99m}Tc-MAA activity to arrive in the lungs and, on the tomographic images, evaluate the distribution of the ^{99m}Tc-MAA. When lung shunting is identified, the cumulative pulmonary dose must be calculated along with the hepatic treatment doses. Pulmonary doses > 30 Gy per treatment or > 50 Gy cumulatively have been associated with the development of radiation pneumonitis.[21]

Dosimetry

Glass microspheres (TheraSphere, BTG, London, UK) are the only radioembolization product to have received FDA approval for the treatment of unresectable HCC.[10] For glass-microsphere dosimetry, the volume that is measured and used in the dosimetry calculation is the volume of liver tissue that is perfused by the hepatic artery branch infused.

Glass microspheres are available in vials with different activities, which are dispensed weekly by the manufacturer. The recommended activity to be administered to a tumor-containing hepatic lobe should correspond to a dose between 80 and 150 Gy, depending on the severity of underlying liver disease. The most commonly used dose range at our institution is between 100 and 120 Gy. Activity required to deliver the desired dose can be calculated by

$$A = \frac{D \times M}{50 \times \left(1 - \frac{\%LSF}{100}\right) \times \left(1 - \frac{\%R}{100}\right)}$$

Activity is measured in GBq infused to the target liver, D is the absorbed dose (Gy) to the target liver mass, M (kg). Liver volume (mL) is calculated with 3D software and converted to mass using a conversion factor of 1.03 mg/mL. Lung-shunt fraction (%LSF) is calculated from nuclear medicine images acquired following the initial mapping angiography. Residual activity within the vial (%R) is measured after ^{90}Y microsphere administration and approximated to be 2% for pretreatment dosing calculations.[22]

Resin microsphere dosimetry can be calculated using body surface area and estimates of tumor burden according to the equation

$$A = BSA - 0.2 + \frac{\%Tumor\ involvement}{100}$$

Activity is GBq infused and BSA is the body surface area in m^2. For resin microsphere dosimetry calculation, activity is decreased depending on the degree of LSF: $< 10\%$ LSF—no reduction; 10-15% LSF—20% reduction; 15-20% LSF—40% reduction; $> 20\%$ LSF—no treatment.[23]