Radioembolization with ^{90}Yttrium Microspheres: A State-of-the-Art Brachytherapy Treatment for Primary and Secondary Liver Malignancies

Part 1: Technical and Methodologic Considerations

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Microsphere and particle technology represent the next-generation agents that have formed the basis of interventional oncology, an evolving subspecialty of interventional radiology. One of these platforms, yttrium-90 microspheres, is rapidly being adopted in the medical community as an adjunctive therapeutic tool in the management of primary and secondary liver malignancies. Given the complexity of the treatment algorithm of patients who may be candidates for this therapy and the need for clinical guidance, a comprehensive review of the methodologic and technical considerations was undertaken. This experience is based on more than 900 ^{90}Y infusions performed over a 5-year period.

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Abbreviations: ECOG = Eastern Cooperative Oncology Group, FDA = Food and Drug Administration, GDA = gastroduodenal artery, HCC = hepatocellular carcinoma, LSF = lung shunt fraction, MAA = macroaggregated albumin, PET = positron emission tomography, PS = performance status, SPECT = single photon emission computed tomography, TACE = transcatheter arterial chemoembolization

YTTRIUM-90 microspheres are 20- to 40-μm particles that emit β-radiation. Because the microspheres are delivered via the hepatic arterial route, the process can be considered as internal rather than external radiation. The treatment algorithm is analogous to that followed with transarterial chemoembolization (TACE). Clinical history, physical examination, laboratory values, and performance status (PS) are evaluated. Patients' conditions are initially evaluated and their disease is staged with cross-sectional imaging techniques: computed tomography (CT), magnetic resonance (MR) imaging, and/or positron emission tomography (PET). When a patient is considered a possible candidate for therapy, evaluation with mesenteric angiography followed by treatment on a lobar basis is undertaken. Patients are followed up clinically to assess toxicities and response before treatment of the other lobe is undertaken.

TheraSphere (glass microsphere; MDS Nordion, Kanata, ON, Canada) was approved in 1999 by the U. S. Food and Drug Administration (FDA) under a humanitarian device exemption for the treatment of unresectable hepatocellular carcinoma (HCC) in patients who can have appropriately positioned hepatic arterial catheters (1). Medical professionals are directed to published FDA guidance documents on humanitarian device exemptions for uses in diseases other than HCC (2). SIR-Spheres (resin microsphere; Sirtex Medical, Lane Cove, Australia) were granted full premarketing approval in 2002 by the FDA for the treatment of colorectal metastases in conjunction with intrahepatic floxuridine (3). Given the dearth of published literature on the technical and methodologic considerations required for proper ^{90}Y implementation and usage, this comprehensive overview was undertaken. For the purposes of this article, unless otherwise stated, ^{90}Y microspheres, radioembolization, and selective internal radiation therapy will refer to the use of TheraSphere and SIR-Spheres.

The use of ^{90}Y for the primary and secondary treatment of liver malignancies is not investigational or experimental (2). Given the FDA approval for both devices, their use in HCC and colorectal cancer represents their approved indication. For disease states other than the strict indication, the use of ^{90}Y represents the practice of medicine. This article is the first of a series of three that will be published on the topic of radioembolization. The first part will focus on the technical and methodologic considerations. The second will discuss special topics as they relate to ^{90}Y microspheres. The third will provide a comprehensive literature review on the topic of radioembo-

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lization and discuss future directions for this technology. It should be noted that some of the discussions presented in parts 1 and 2 represent the opinions of the authors, whereas part 3 represents a strict review of the literature. This experience is based on more than 900 ^{90}Y infusions performed over a 5-year period by a multidisciplinary team including investigators from medical oncology, hepatology, surgery, transplantation, and interventional radiology as the authorized users.

TECHNICAL AND METHODOLOGIC CONSIDERATIONS

Overview

Radioembolization is defined as the injection of micron-sized embolic particles loaded with a radioisotope by use of percutaneous transarterial techniques. There are two distinct aspects to the procedure. The first is the injection of embolic particles (ie, "embolization") as the vehicle; the second is the delivery and administration via this embolic vehicle of radiation ("radio-"). Fluoroscopic guidance, angiographic endpoints of embolization and stasis, and the need to modify this on the basis of angiographic findings make this treatment a true embolization procedure. In addition, dosimetry planning, the administration and delivery of radiation, modification of dose on the basis of tumor and hepatic volume, and the required knowledge of radiation effects on tissue make this a brachytherapy procedure as well. Although the term "selective internal radiation therapy" has also been used to describe this therapy, "radioembolization" more accurately describes the actual mode of action of ^{90}Y microspheres according to the rationale described. Hence, for technologies that require embolic particles to carry radioisotopes to the targeted tumors, we propose that the term "radioembolization" be formally recognized.

HCC represents one of the most common forms of cancer, with more than 1 million new cases estimated annually worldwide. In the United States, the incidence of HCC has steadily increased during the past two decades, an estimated 18,900 new cases having been diagnosed in 2004 (4). Traditionally, these patients have had few treatment options (5). The safety and therapeutic benefit of ^{90}Y microspheres for HCC is well documented in the literature (6–8).

The evaluation of unresectable HCC is significantly different from that of metastatic disease. Curative options include liver transplantation and resection (9). Unfortunately, only 10%–15% of patients are candidates for curative therapy (9). Ideal candidates for treatment with ^{90}Y microspheres include patients with a performance status (PS) of 0–2, intact liver function, and a patent portal vein. Unlike patients with metastatic disease to the liver, pathologic confirmation of HCC is not always necessary and may be established in patients with classic history (ie, alcohol or viral hepatitis), imaging findings (ie, hypervascular tumors, cirrhosis) and a serum α-fetoprotein level greater than 400 ng/mL (10). The benefits of radioembolization with ^{90}Y in patients with HCC has been previously described (7,11–19).

Patients with metastatic cancer to the liver often have complex medical histories. In cases of colon cancer, if the disease is detected in the early stages, resection of the primary tumor without lymph node involvement may obtain long-term cure. In some cases, patients with stage IV disease with liver metastases may be treated with surgical resection alone, also providing a chance for long-term cure. In patients with surgically unresectable liver disease with or without extrahepatic disease, systemic chemotherapy has become the standard for first- and second-line treatment (20,21). Combination therapy with angiogenesis inhibitors and surgical resection has now become an integral part of first- and second-line therapies (22). Patients with liver-dominant disease in which standard first- and second-line therapies have failed may be considered for treatment with ^{90}Y.

The liver is the most frequent site of metastases, primarily as a result of the spread of cancer cells through the portal circulation. In fact, approximately 60% of patients with colorectal carcinoma eventually have liver disease as the predominant site (23). Similarly to HCC, surgical resection of metastatic hepatic disease is the treatment of choice. However, surgical resection is feasible in fewer than 20% of patients (23). The benefits of radioembolization with ^{90}Y in these patients has been reported in many studies (24–29).

PATIENT SCREENING AND SELECTION

Clinical Presentation and Imaging Correlates in HCC

The selection process for patients undergoing ^{90}Y treatment is multifactorial. Simply put, ideal patients should have liver-only or liver-dominant disease, minimal comorbidities, and normal liver function test results. Patients with HCC may have a clinical history of viral (hepatitis B or C virus) or alcoholic cirrhosis. In rare instances, patients may present with cirrhosis of uncertain cause, a condition often referred to as nonalcoholic steatohepatitis (30). Depending on the severity of the disease, patients can manifest other sequelae of cirrhosis such as encephalopathy, ascites, and portal hypertension with or without portal vein thrombosis. Patients with HCC may have varied surgical and therapeutic histories, including previous resection, radiofrequency ablation, or TACE. Clinical considerations in these patients include the degree of hepatic compromise and imaging findings.

Hepatoma findings on imaging are quite variable (31). If ultrasound (US) is the initial diagnostic modality, additional cross-sectional imaging should be performed. Other than operator dependence, altered hepatic echotexture can result in a high false-negative rate, especially for smaller lesions. Also, in some cases, infiltrative tumors can be misdiagnosed as peliosis hepatis (32). For patients with cirrhosis, any hepatic mass should be considered a hepatoma until proven otherwise, warranting further investigation. Triple-phase CT is highly sensitive in the detection of hepatoma (33). Because many of these tumors are hypervascular, scanning in the early phases allows for detection. Later-phase imaging is necessary to detect other less vascular lesions and multifocality, as well as to identify portal vein patency (33). Alternatively, MR imaging can also be used to identify and characterize HCC lesions, with specific attention to diffusion-weighted imaging sequences and oxygenation (34,35). The diagnosis of