

## The Clinical Value of Radioembolization in the Treatment of Inoperable Liver Cancer

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### Abstract

Hepatocellular carcinoma (HCC) is a common malignancy worldwide. HCC-related mortality is high because most cases are diagnosed at an advanced stage. HCCs are relatively resistant to radiation and the liver is unable to tolerate the radiation doses required to achieve tumoricidal effects by standard external-beam radiation. Focal radiation techniques employing a 3D approach have been shown to safely permit higher levels of radiation to targeted regions within the liver. Delivery of therapy through hepatic artery branches preferentially affects HCC tumors and spares the surrounding liver parenchyma. Selective targeting of radionuclides to tumors has been shown to achieve high radiation dose ratios. Transarterial radionuclide therapies have been developed with the objective of achieving selective intra-arterial delivery of radiotherapy, including radioactive iodine-131 (<sup>131</sup>I), rhenium-188 (<sup>188</sup>Re), yttrium-90 (<sup>90</sup>Y) (resin or glass microspheres), and others. These treatments have been used to treat HCC via a selective transarterial approach as an alternative to TACE. Portal vein thrombosis (PVT) is a relative contraindication to transarterial chemoembolization (TACE); in contrast, high specific activity radiomicrospheres do not occlude a significant portion of the hepatic arterial vascular bed and can therefore be used in patients with PVT. The devices, toxicities, and results with use of the available radioembolic devices are reviewed in this article.

### Keywords

Inoperable hepatocellular carcinoma, portal vein thrombosis, radioembolization, radioactive iodine-131, rhenium-188, Theraspheres®, transarterial radionuclide therapies, yttrium-90

**Disclosure:** Laura E Moreno-Luna, MD, and James C Andrews, MD, have no conflicts of interest to declare. Lewis R Roberts, MB, ChB, PhD, receives grant support from MDS Nordion.

**Received:** December 1, 2008 **Accepted:** May 5, 2009 **DOI:** 10.17925/OHR.2009.05.1.65

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Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third most common cause of death from cancer worldwide.<sup>1</sup> The incidence of HCC in the US is increasing because of the rise in the prevalence of hepatitis C virus infection.<sup>2,3</sup> HCC-related mortality is high because most cases are diagnosed at an advanced stage, when potentially curative therapies such as liver transplantation, surgical resection, and local ablation are not feasible.<sup>4-7</sup> The majority of patients are therefore candidates for palliative therapies only.<sup>8</sup> Due to the capacity of liver cells to detoxify and excrete drugs, HCCs are relatively resistant to chemotherapy; in addition, the splenomegaly and cytopenias associated with cirrhosis with portal hypertension render patients prone to systemic chemotherapy-related toxicity.<sup>9</sup> Transarterial chemoembolization (TACE) is a loco-regional therapy that delivers high doses of chemotherapy to HCCs through the hepatic artery, with limited systemic effect. TACE has been proven to improve survival of patients with unresectable HCC without portal vein thrombosis (PVT).<sup>10-12</sup> Recently, a number of devices for transarterial radioembolization (TARE) have been tested for treatment of HCC in early-phase studies. This article will summarize the results thus far, with an emphasis on yttrium-90 (<sup>90</sup>Y) radioactive glass microspheres, which are the only modality currently approved for use in the US.

### Theoretical Considerations

The liver parenchyma is relatively sensitive to radiation, with a tolerance to external irradiation of approximately 30Gy.<sup>13,14</sup> In contrast, HCCs are relatively resistant to radiation, requiring doses of 120Gy for tumoricidal effect. The liver is unable to tolerate the radiation doses required to achieve tumoricidal effects by standard external-beam radiation; therefore, whole-liver external-beam radiation therapy is of limited utility in the treatment of unresectable HCC.<sup>15</sup> Several studies have confirmed that focal radiation techniques employing a 3D approach instead of broad axial-plane techniques safely permit higher levels of radiation to targeted regions within the liver.<sup>5,16</sup> HCC tumors are highly vascular and receive almost all of their blood supply (95–100%) from the hepatic artery, in contrast to the normal liver parenchyma, which is primarily supplied by the portal vein (75–85%).<sup>15</sup> Consequently, delivery of therapy through hepatic artery branches preferentially affects HCC tumors and spares the surrounding liver parenchyma. Selective targeting of radionuclides to tumors has been shown to achieve radiation dose ratios (tumor to benign liver) of up to 25–30 to 1.<sup>17</sup> Portal vein occlusion is considered a relative contraindication to TACE. The high-specific-activity radioembolization microspheres do not occlude a significant portion of the hepatic

arterial vascular bed and can therefore be used in patients with portal vein thrombosis.<sup>9</sup> Different transarterial radionuclide therapies have been developed with the objective of achieving selective intra-arterial delivery of radiotherapy, including radioactive iodine-131 (<sup>131</sup>I), rhenium-188 (<sup>188</sup>Re), <sup>90</sup>Y (resin or glass microspheres),<sup>6,18-21</sup> and others.<sup>22</sup> All of these treatments have been used to treat HCC via a selective transarterial approach as an alternative to TACE. In this article, we will review the devices, toxicities, and results with use of the currently available radioembolic devices.

## Iodine-131-based Devices

<sup>131</sup>I was the first radionuclide to have significant use as an intra-arterial therapy for HCC.<sup>23-25</sup> <sup>131</sup>I is a  $\gamma$ -emitter with a relatively long half-life of 8.04 days and a maximum energy of 0.364MeV, and achieves a mean tissue penetration of 0.4mm. <sup>131</sup>I is most frequently used by exchange with the iodine moiety of lipiodol, a preparation of iodized poppyseed oil (Lipiodol®). Arterially administered lipiodol leaks out of vascular spaces and localizes in the tumor cell membrane and intracellular compartment.<sup>26</sup> Non-radioactive iodine is administered before treatment to saturate thyroid uptake and prevent the uptake of circulating radioisotope into the thyroid gland. <sup>131</sup>I–lipiodol has been used for treatment of unresectable HCCs, in the adjuvant setting after surgical resection, and also prior to surgical resection or liver transplantation. Randomized controlled trials in the adjuvant setting have shown statistically significant decreases in recurrence rate and

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improvements in overall survival in patients receiving <sup>131</sup>I–lipiodol radioembolization after surgical resection.<sup>27,28</sup> Pre-surgical administration has confirmed the ability of <sup>131</sup>I–lipiodol to produce partial and complete tumor necrosis of resected or explanted tumors.<sup>29</sup> Because it does not occlude arterial flow, <sup>131</sup>I–lipiodol radioembolization has also been used in patients with unresectable HCC and portal vein thrombosis and has demonstrated significantly improved survival compared with best supportive care.<sup>30</sup> Tumor response rates after <sup>131</sup>I–lipiodol therapy range from 17 to 92%.<sup>31</sup> A number of other <sup>131</sup>I complexes have also been used, including radioimmunotherapy with <sup>131</sup>I antiferritin<sup>32</sup> and <sup>131</sup>I–anti-HAb18G/CD147 (<sup>131</sup>I metuximab/licartin), which targets the human HCC-associated antigen HAb18G/CD147.<sup>33-35</sup>

The major side effects of <sup>131</sup>I radioembolization have included liver failure and interstitial pneumonitis, in some instances leading to premature death. Compared with TACE, <sup>131</sup>I–lipiodol radioembolization showed equivalent efficacy and was significantly better tolerated.<sup>36</sup> However, <sup>131</sup>I–lipiodol and other <sup>131</sup>I-based devices have the significant

limitation that because of the high-energy  $\gamma$ -irradiation they produce, patients require several days of hospitalization with limited contact in a radiation-shielded room. This limits the applicability of this therapy in many of the clinical settings in which radioembolization would potentially be of utility. An advantage of <sup>131</sup>I–lipiodol over early formulations of <sup>90</sup>Y-based radioembolization devices is that iodine is an integral constituent of lipiodol, hence <sup>131</sup>I–lipiodol is produced by isotopic exchange and the radioisotope remains a stable constituent of the lipiodol, limiting leaching and unintended systemic therapy; in contrast, early <sup>90</sup>Y devices had high rates of leaching of <sup>90</sup>Y from the compounds, resulting in significant bone marrow toxicity.<sup>37</sup>

## Rhenium-188-based Devices

<sup>188</sup>Re has been used to treat unresectable and recurrent HCC.<sup>19,38-41</sup> <sup>188</sup>Re is a  $\beta$ -emitter with a short half-life of 16.9 hours and a high maximum energy of 2.12MeV, which is effective for antitumor therapy. The average tissue penetration is 2.6mm, with a maximum range of 10.1mm. The  $\beta$ -particles are completely attenuated beyond this range, thus limiting injury to adjacent benign tissues and organs and allowing outpatient treatment without extensive radiation shielding or other precautions. <sup>188</sup>Re also has a  $\gamma$ -emission of 155keV (15% abundance); this energy is close to that of <sup>99m</sup>Tc and thus allows performance of pre- and post-therapy  $\gamma$ -camera scans for biodistribution and dosimetry studies. A major advantage of <sup>188</sup>Re is that it is available through the use of a generator that has a useful shelf-life of several months, in comparison with other radionuclide devices that have a shelf-life of only days. The availability of <sup>188</sup>Re in a generator form makes its storage, transportation, elution, and usage very convenient and cost-effective, particularly at remote sites and in developing countries.<sup>42</sup> The use of a generator also makes <sup>188</sup>Re available on a constant and need-to-use basis.<sup>40</sup> <sup>188</sup>Re has been delivered in two different formulations: as radiolabeled biodegradable human serum albumin microspheres with a mean diameter of 20–25 $\mu$ m,<sup>43,44</sup> and as a stable conjugate to lipiodol using 4-hexadecyl-1-2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol (HDD).<sup>45</sup> A number of phase I and II studies performed using both formulations suggest that they are both effective in achieving complete or partial tumor ablation or stable disease in the majority of HCC patients, with survival rates in patients with Child-Pugh class A and B liver disease that are similar to the rates achieved using chemoembolization. There have been no randomized controlled trials of these devices in comparison with best supportive care only or with TACE; such trials are required to confirm the presumed efficacy and relative safety of both formulations.<sup>41,46-50</sup>

## Yttrium-90-based Devices

Promising results have been reported with <sup>90</sup>Y glass microspheres (Theraspheres®) for treatment of HCC. The use of <sup>90</sup>Y glass microspheres was approved by the US Food and Drug Administration (FDA) in 2001 for treatment of unresectable HCC. In the US, <sup>90</sup>Y glass microspheres are currently being used at over 60 medical centers.<sup>5</sup> Most commonly, patients are considered for <sup>90</sup>Y therapy only if they are not candidates for surgical resection or percutaneous ablation; however, increasing experience is developing with patients for whom <sup>90</sup>Y microsphere therapy is performed for tumor downstaging or prevention of tumor progression prior to liver transplantation.<sup>5</sup> The microspheres are initially produced as insoluble glass microspheres

in which inert  $^{89}\text{Y}$  is an integral constituent of the glass. Prior to shipment to the treating site, the microspheres are neutron-bombarded to convert the  $^{89}\text{Y}$  to  $^{90}\text{Y}$ .  $^{90}\text{Y}$  is a  $\beta$ -emitter with a half-life of 63 hours, a mean tissue penetrance of 2.5mm, and a maximum radius of action of 1cm ( $\pm 2.5\text{mm}$ ). The microspheres have a mean diameter of  $25\mu\text{m}$  ( $\pm 10\mu\text{m}$ ). Each milligram contains between 22,000 and 73,000 microspheres and can deliver up to 150Gy.<sup>51-53</sup>

### Technical Considerations

$^{90}\text{Y}$  microspheres are delivered into the liver tumor through a catheter placed percutaneously into the hepatic artery. Lobar, segmental, or subsegmental treatment can be performed. Since the hepatic artery provides the main blood supply to HCCs, there is preferential deposition of the microspheres in the tumor, in contrast to the normal liver parenchyma, which receives blood supply primarily from the portal vein. The  $^{90}\text{Y}$  microspheres are entrapped within the tumor and exert a local  $\beta$ -radiation effect. The microspheres are not biodegradable and do not redistribute to other organs of the body.<sup>5,6,54</sup>

### Patient Selection and Evaluation

The pre-treatment patient evaluation includes a clinical history and physical examination. Diagnostic laboratory studies usually performed within 30 days of treatment include a complete blood count with differential, prothrombin time, partial thromboplastin time and serum chemistry (electrolytes, aspartate aminotransferase [AST], alanine aminotransferase [ALT], creatinine, blood urea nitrogen [BUN], alkaline phosphatase, albumin, total bilirubin, pseudocholinesterase, and alpha fetoprotein). Diagnostic imaging studies include a chest X-ray, computed tomography (CT) scan of the chest and abdomen to

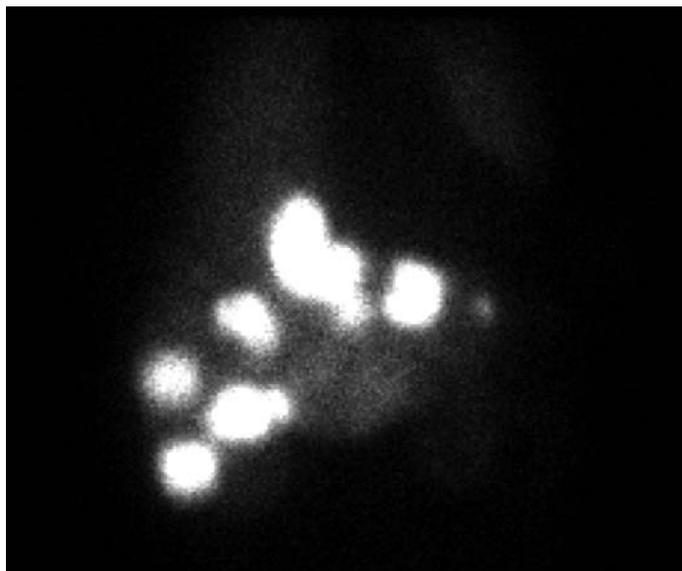
*The arteriovenous shunting occurs in the tumors, and the patients at highest risk for exclusion due to lung shunt are those with large tumor volumes and those with hepatic venous tumor thrombus.*

calculate the volume of each liver lobe necessary to determine the  $^{90}\text{Y}$  dose, and hepatic angiography to define the vascular anatomy. If there are hepatic arterial branches identified at the time of the staging angiogram that would lead to extrahepatic deposition of the microspheres (most commonly right gastric or gastroduodenal arteries), these are occluded using standard angiographic techniques. A technetium-99m MAA study is then performed to calculate the percentage of radiation that would be shunted to the lungs (see Figure 1).

### Contraindications and Recommendations

The use of  $^{90}\text{Y}$  radioembolization is contraindicated in patients whose angiogram shows shunting of blood to the gastrointestinal tract that cannot be corrected by angiographic techniques, and patients whose technetium-99m MAA hepatic arterial perfusion scintigraphy shows significant shunting of blood to the lungs that could result in a delivery

**Figure 1: Hepatic Artery Perfusion Scan, Anterior View, After Injecting  $^{99\text{m}}\text{Tc}$ -macro-aggregated Albumin into the Proper Hepatic Artery**



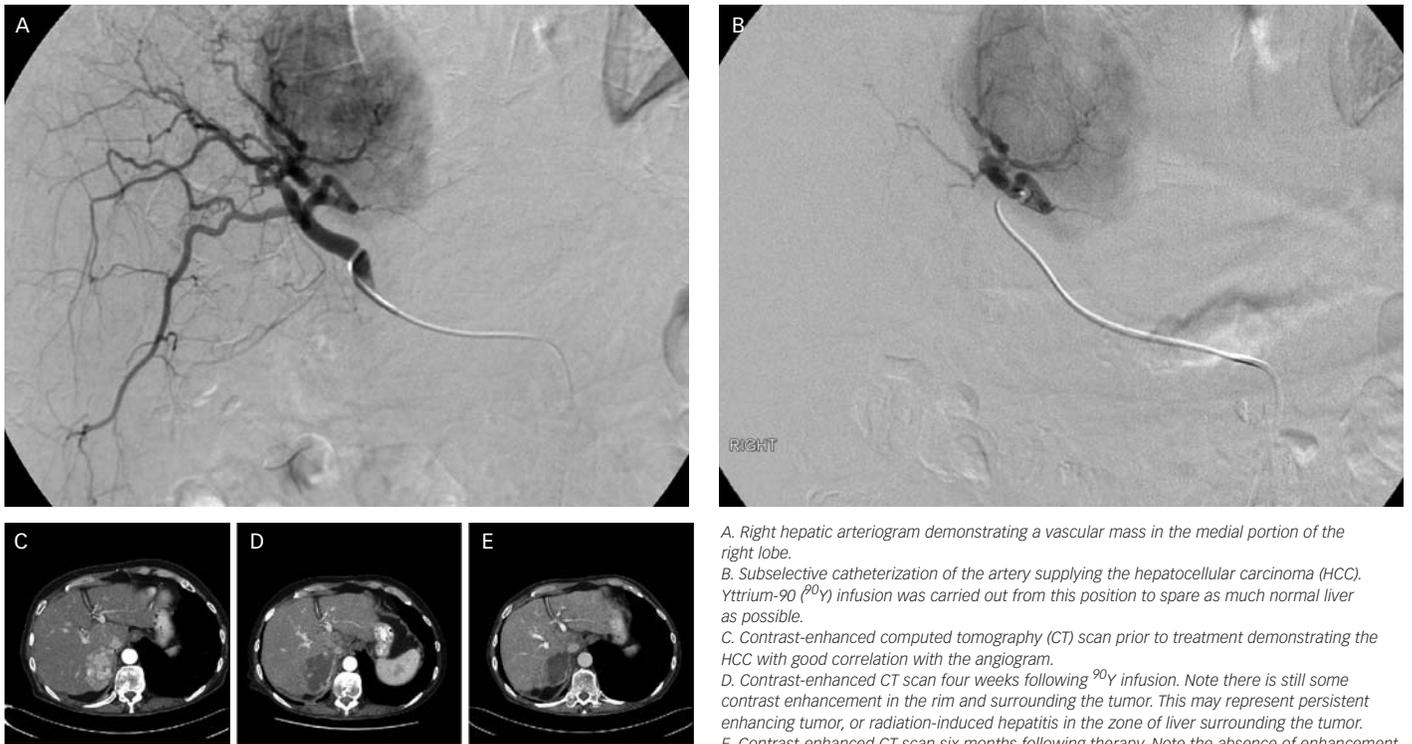
*Note the intense localization of the MAA in the tumor nodules in this patient with multifocal hepatocellular carcinoma compared with the surrounding liver. This should correlate with the relatively greater deposition of the therapeutic microspheres within the tumors. Also note the small amount of activity that reached the lungs by way of arteriovenous shunts through the tumors.*

of greater than 16.5mCi of radiation to the lungs. Radiation pneumonitis has been seen in patients with shunting that has resulted in doses to the lungs of greater than 30Gy in a single treatment. The arteriovenous shunting occurs in the tumors, and the patients at highest risk for exclusion due to lung shunt are those with large tumor volumes and those with hepatic venous tumor thrombus.  $^{90}\text{Y}$  microspheres are also contraindicated in patients in whom hepatic artery catheterization shows vascular abnormalities, in those with bleeding diathesis, and allergy to contrast dye. Its use is not recommended for treatment in patients with renal insufficiency, pulmonary insufficiency, and/or severe liver dysfunction. Some authors suggest patients should have bilirubin  $\leq 2.0\text{mg/dl}$  and creatinine  $\leq 2.0\text{mg/dl}$  at the time of treatment, and it is contraindicated in pregnancy.<sup>52,53</sup>

### Efficacy

The response of  $^{90}\text{Y}$  microspheres in patients diagnosed with unresectable HCC is encouraging for patients with good functional performance, liver reserve, and no main portal vein thrombosis (PVT) (see Figure 2). Geshwind et al. reported that Cancer of the Liver Italian Program (CLIP) categories were statistically associated ( $p=0.002$ ) with survival, as indicated by the association of better prognostic CLIP scores with increasing survival. They also found a difference in survival in patients with Child A versus B ( $p=0.007$ ) and alpha-fetoprotein  $<400$  versus  $\geq 400\text{ng/ml}$  ( $p=0.003$ ). For this group of patients, the estimated median survival times and the one-year survival rates were 628 days and 63% for Okuda stage I patients and 384 days and 51% for Okuda stage II patients ( $p=0.02$ ; log-rank test).<sup>6</sup> Because of the absence of vascular occlusion with  $^{90}\text{Y}$  microsphere therapy, patients with PVT remain candidates for this therapy. Kulik et al. reported a study in which they compared the use of  $^{90}\text{Y}$  in patients with HCC with and without PVT.

**Figure 2: Technique and Results of Yttrium-90 Transarterial Radioembolization**



A. Right hepatic arteriogram demonstrating a vascular mass in the medial portion of the right lobe.  
 B. Subselective catheterization of the artery supplying the hepatocellular carcinoma (HCC). Yttrium-90 ( $^{90}\text{Y}$ ) infusion was carried out from this position to spare as much normal liver as possible.  
 C. Contrast-enhanced computed tomography (CT) scan prior to treatment demonstrating the HCC with good correlation with the angiogram.  
 D. Contrast-enhanced CT scan four weeks following  $^{90}\text{Y}$  infusion. Note there is still some contrast enhancement in the rim and surrounding the tumor. This may represent persistent enhancing tumor, or radiation-induced hepatitis in the zone of liver surrounding the tumor.  
 E. Contrast-enhanced CT scan six months following therapy. Note the absence of enhancement in the tumor. There is a small degree of tumor shrinkage as well.

For their entire 108-patient cohort, a significant trend toward longer median survival was seen in the non-PVT group (467 days, 15.6 months) compared with the others ( $p=0.005$ ). Interestingly, this trend was not maintained in the group of patients with cirrhosis (385 days, 12.8 months;  $p=0.10$ ), but was maintained in patients without cirrhosis ( $p=0.02$ ). The authors concluded that patients without cirrhosis and without PVT had the highest survival observed in the study (813 days, 27.1 months;  $p=0.02$ ).<sup>53</sup>

It has also been reported that in a 150-patient cohort with unresectable HCC, treated with  $^{90}\text{Y}$  microspheres, 19 of 34 patients with UNOS stage T3 disease and available pre- and post-treatment imaging were successfully downstaged to T2. When analyzed as a cohort, the 34 patients had a

eight of 34 patients were transplanted. In this group of patients the overall survival was 84, 54, and 27% at one, two, and three years, respectively. Median survival for the entire 35-patient cohort was 800 days.<sup>5</sup> We reported the case of a patient who is alive and remains tumor-free 24 months post-orthotopic liver transplantation (OLT) after  $^{90}\text{Y}$  microsphere radioembolization applied for treatment of a large HCC.<sup>55</sup>

## Adverse Events

Based on clinical experience with  $^{90}\text{Y}$  microspheres, certain possible adverse reactions have been identified. In previous studies some of these adverse events were reported as severe, and few of them have been life-threatening or fatal. Clinical adverse events have been classified into hepatic (hyperbilirubinemia, ascites, increased aminotransferases, alkaline phosphatase, prothrombin time, encephalopathy, liver failure), gastrointestinal (gastric/duodenal ulcer, nausea, cholecystitis), hematological (lymphopenia), pulmonary (pleural effusion and aspiration pneumonia), renal (hepatorenal syndrome), circulatory (edema, hypotension, hypertension), infectious (spontaneous bacterial peritonitis), and others (allergic reaction, hyponatremia, fatigue, malaise, fall).<sup>6,51,53,56</sup> Kulik et al. reported that 9% of patients had vague abdominal pain. In this cohort of patients there were no significant complications or mortalities at either treatment center secondary to the technical aspects of radioembolization; nevertheless, there was one death in the follow-up period that was possibly attributed to treatment. Geschwind et al. studied an 80-patient cohort and reported that 22 patients (28%) had at least one hepatic event, four patients (5%) had at least one gastrointestinal event, and 10 patients (13%) had at least one pain event associated with  $^{90}\text{Y}$  microsphere treatment. Of the 80 patients, only eight had life-threatening events and

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significant decrease in tumor size ( $p<0.0001$ ). The median pre-treatment tumor size was 5.6cm and the median post-treatment tumor size was 4.3cm. The median reduction in tumor size for all 34 patients was 49%. The authors report one patient who underwent right hepatectomy 40 days following treatment; 11 of 34 patients were downstaged to RFA and

only one had a fatal event caused by liver failure; however, the cause remained obscure since the liver biopsy before death was inconclusive for radiation-induced liver disease.<sup>6</sup> In 2005, Goin et al. compared TACE (29 patients) and <sup>90</sup>Y microspheres (34 patients) for post-embolization syndrome (PES) manifested by post-treatment abdominal pain, nausea, vomiting, and fever in the absence of infection. The incidence of PES was nearly four times higher in the TACE group (p=0.003; 95% confidence interval [CI] 1.6–16.3), suggesting a favorable toxicity profile for radioembolization in this tumor type.<sup>7,15,57</sup>

### Quality of Life

Quality of life for patients with HCC is a difficult subject, since treatment options are limited and the likelihood of cure is low and, as previously mentioned, very often patients are diagnosed at advanced stages of the disease. Few studies have evaluated patient health-related quality of life (HRQoL) in patients with treated HCC. In 2004, Steel et al. evaluated HRQoL in patients with primary HCC who received either hepatic arterial infusion (HAI) of cisplatin or <sup>90</sup>Y. In this study, patients treated with <sup>90</sup>Y reported significantly higher scores on scales measuring functional wellbeing (p<0.001) and overall HRQoL (p<0.001) compared with those treated with cisplatin. At six-month follow-up, patients treated with <sup>90</sup>Y reported significantly higher functional wellbeing than patients treated with cisplatin (p<0.04); however, the overall HRQoL was no longer significantly different between the two treatment groups. The results of this study were consistent with previous reports that suggest HAI of chemotherapy is better tolerated than systemic chemotherapy.<sup>58,59</sup> HAI of <sup>90</sup>Y microspheres demonstrated a slight advantage over HAI of cisplatin with regard to HRQoL even when patients with HAI of cisplatin reported a significantly higher functional and overall HRQoL at baseline.<sup>58</sup> A major contributor to the improved quality of life of patients receiving <sup>90</sup>Y microsphere radioembolization is the absence of an embolic effect to the hepatic artery distribution. This results in minimal abdominal pain or tumor lysis after therapy and consequently the therapy is usually accomplished as an outpatient procedure.

### Conclusions

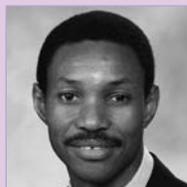
Intra-arterial radionuclide therapies have recently shown promising results for the treatment of patients with unresectable HCC, with

acceptable levels of toxicity. Early results also suggest potential utility for treatment of patients on the waiting list for liver transplantation and for downstaging patients with disease that is beyond the standard Milan criteria and perhaps even beyond the University of California, San Francisco (UCSF) criteria for liver transplantation.

There are a number of challenges that remain before radioembolization can be considered a fully validated therapy for HCC. It is important to perform randomized controlled trials of TARE in comparison with TACE, which has been proven to improve outcomes of patients with unresectable HCC without PVT. It is also important to identify predictive variables for those patients who are most likely to develop toxicity and side effects after TARE in order to minimize toxicity. Additional studies to improve our understanding of the relative perfusion of radioactive microspheres to tumor versus benign liver and the ideal dosimetry techniques to optimize tumor kill while sparing the surrounding liver are critically needed. Nevertheless, the early results give considerable optimism for the eventual establishment of TARE as a valuable component of our armamentarium for effective therapy of HCC. ■

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