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ORIGINAL ARTICLE

Radioembolization for the treatment of unresectable liver cancer: initial experience at a single center

Bora Peynircioğlu, Barbaros Çil, Fani Bozkurt, Ece Aydemir, Ömer Uğur, Ferhun Balkancı

PURPOSE
Radioembolization with yttrium-90 microsphere (Y-90) therapy with SIR-Spheres® (Sirtex Medical, Lane Cove, Australia) was approved by the Turkish Ministry of Health in April 2008. In this study, we present the preliminary experience at a tertiary care center with early follow-up results of Y-90 therapy, as well as a review of the related literature.

MATERIALS AND METHODS
Complete evaluation for radioembolization was performed in 10 patients (8 males, 2 females; mean age, 52.3 years) during an 8-month period at a single center, of which 9 were actually treated with SIR-Spheres®. All patients underwent meticulous pre- and post-procedural imaging studies to document the therapy response.

RESULTS
In order to isolate the target hepatic arterial circulation, following branches were embolized as they were considered as potential gastrointestinal shunts: the gastroduodenal artery (n = 5), right gastric artery (n = 1), and supraduodenal artery (n = 1). Radioembolization therapy could not be performed only in one patient because of a hepatogastric shunt of unknown origin. No significant hepatopulmonary shunting was identified (maximum, 9% shunting). The body surface area method was used to calculate the Y-90 dose in all patients (mean dose, 1.24 GBq). All patients had at least partial response of the targeted liver lesions, according to RECIST (Response Evaluation Criteria in Solid Tumors).

CONCLUSION
In comparison to chemoembolization, radioembolization has less systemic toxicity and can be performed as an outpatient procedure, which makes it more attractive to both patients and physicians. From our limited experience, the radioembolization procedure is a promising first-line treatment in unresectable liver cancer; randomized controlled multi-center studies, however, are needed.

Key words: • *therapeutic embolizations* • *yttrium radioisotopes* • *liver neoplasms*

From the Departments of Radiology (B.P. ✉ *borapeynir@gmail.com*, B.Ç., E.A., F.Balkancı), and Nuclear Medicine (F.Bozkurt, Ö.U.), Hacettepe University School of Medicine, Ankara, Turkey.

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Unresectable liver cancer from primary or metastatic cancer causes significant suffering and eventual death in many patients worldwide each year. Yttrium-90 microsphere (Y-90) therapy for hepatic tumors—so-called radioembolization—has been increasingly used in the last decade, although its first clinical trials date back to the early 1960s (1). Transarterial treatment of liver tumors has been performed for 30 years all over the world. Chemoembolization was first introduced in the late 1970s; today, transarterial chemoembolization (TACE) is a widely accepted treatment technique for patients with uncontrolled hepatocellular cancer (HCC) or metastatic liver cancer primarily caused by colo-rectal carcinoma. Radioembolization, a new form of transarterial therapy involving infusion of radioactive microparticles, has shown promise for the treatment of patients with unresectable liver tumors (2–7). The therapeutic advantage of the hepatic arterial approach is based on the unique dual vascular supply of the liver. It is known that hepatic tumors receive 80–100% of afferent blood exclusively from the hepatic artery (8). Radioembolization takes advantage of this to provide liver-directed transarterial therapy. There are two distinct aspects of the procedure: the first being the injection of embolic particles ("embolization") as the vehicle and the second being the delivery and administration, via this embolic vehicle, of radiation ("radio").

The Y-90 microsphere therapy with SIR-Spheres® (Sirtex Medical, Lane Cove, Australia) was approved by the Turkish Ministry of Health in April 2008. Since then, increasing numbers of patients are receiving this treatment in an effort to control or stabilize liver involvement of several different inoperable cancers. In this study, we present the preliminary experience at a single center with early follow-up results of Y-90 therapy, as well as the review of the related literature.

Materials and methods

In this study, complete evaluation for radioembolization procedure was performed in 10 patients (8 males, 2 females; mean age, 52.3 years) who were selected to be treated with radioembolization using SIR-Spheres during an 8-month period between April 2008 and January 2009 at a tertiary care hospital. However, 9 out of 10 patients did receive the actual treatment. In one patient, the radioembolization procedure could not be performed due to a hepatogastric shunt of unknown origin. Liver diseases of all selected patients were inoperable primary or metastatic liver malignancies, including hepatocellular carcinoma (n = 1), cholangiocarcinoma (n = 3), colorectal carcinoma metastases (n = 1), pancreatic adenocarcinoma metastases (n = 1), gastric adenocarcinoma metastases (n = 1), neuroendocrine tumor metastases (n = 1), breast cancer metastases (n = 1), and metastatic adenocarcinoma of unknown origin (n = 1). All patients had undergone other treatments of liver disease prior to

radioembolization, including different chemotherapy regimens and surgical resection. Initial hepatic arteriography with/without visceral artery embolization and Technetium-99m-macroaggregated albumin (Tc-99m-MAA) infusion prior to Y-90 treatment was performed in all patients primarily for isolation of the hepatic artery circulation and to prevent extrahepatic shunting to the lungs and gastrointestinal tract. SIR-Spheres treatment was used in all patients; the TheraSphere (MDS Nordion, Ottawa, Canada) is not yet available in our country. All patients had F-18 fluorodeoxyglucose-positron emission tomography-computed tomography (FDG-PET-CT) and dynamic CT scans before and after Y-90 therapy to determine the cross-sectional and metabolic responses to the treatments.

Patient selection

In general, patient selection criteria for radioembolization are very similar to those for chemoembolization (9). Adequate coagulation parameters and non-compromised pulmonary functions to undergo arterial catheterization and selective visceral catheterization, and adequate liver function as in chemoembolization were sought in all patients. Pre-procedural intravenous hydration with N-acetyl cysteine was administered in patients with impaired renal function (10). Adequate liver function in primary liver tumors was necessary. Additional inclusion criteria were tumor less than 70% of the total liver volume; no evidence of infiltrative disease or complete portal vein thrombosis; total bilirubin level less than 2 mg/dL, and alanine or aspartate amino-transferase levels less than five times the upper limit of normal. Patients with metastatic liver disease should have normal liver function tests and acceptable performance status. Portal vein thrombosis has been regarded as a relative contraindication for such treatments as TACE; however, it is not necessarily a contraindication for radioembolization because relative percentage of obliteration is small and overall embolic effect is minimal (10). Other exclusionary criteria include immediate life-threatening extrahepatic disease, non-correctable flow to the gastrointestinal tract, and hepatopulmonary lung shunting. Being a candidate for liver transplantation is not a contraindication for liver radioembolization; the only concern is the risk of radiation exposure of the surgery team during the transplantation, which can be significantly reduced by waiting at least a month for the surgery after the last radioembolization session. There was no transplant candidate patient in our study group. For SIR-Spheres which were used in all patients in this study, infusion is limited by the lung shunt fraction (contraindicated above 20% shunting). Activity of SIR-Spheres infused is adjusted based on tumor volume and lung shunt fraction (11). For TheraSphere, which is not available in our country yet, the limitation of what can be administered to the lungs is based on cumulative dose, irrespective of lung shunt (12).

Initial angiographic evaluation

An initial angiographic evaluation is a routine practice once a patient has been selected as a candidate for radioembolization. The hepatic arterial anatomy is to be evaluated primarily to identify the anatomic variants, and isolate the hepatic circulation by occluding extrahepatic vessels (13). The technique includes standard visceral angiography using a 4 or 5 French diagnostic catheter. Following an abdominal aortogram, a superior mesenteric artery injection is performed to assess for the presence of accessory or replaced hepatic arteries arising from the superior mesenteric artery. A venous phase is also obtained to evaluate the status/patency of the portal vein. The celiac trunk is selectively catheterized to evaluate the hepatic arterial supply. Subsequent to celiac injection, it is imperative that selective right and left hepatic angiography with power injection angiography be performed, usually with a microcatheter system (Progreat 2.7 F, Somerset, New Jersey, USA). This will allow for the identification of variant mesenteric anatomy and subsequent prophylactic embolization of extrahepatic vessels such as the right gastric, gastroduodenal, or falciform artery. Other vessels that may be identified and may require prophylactic embolization include the supraduodenal, retroduodenal, left inferior phrenic, accessory left gastric, and inferior esophageal artery. Detailed technical protocol for mapping mesenteric angiography prior to radioembolization has already been described in the literature (10).

Once hepatic arterial anatomy is well documented, selective arteriography is performed in the expected location of the Y-90 treatment. To avoid catheter/wire induced vasospasm that may preclude optimal evaluation or treatment, microcatheter injections are recommended, particularly if the vessels are small in caliber or demonstrate significant tortuosity. Following the positioning of the catheter at the desired location, the presence of lung shunting through the tumor must be determined. The lung-shunt fraction is calculated as the fraction of Tc-99m-MAA observed in the lungs relative to the total Tc-99m-MAA activity observed, and can be determined by infusing 5 mCi of Tc-99m labeled MAA particles through the catheter (Fig. 1). MAA particles range in size from 10 to 60 nm, with a mean diameter of 35 nm. The Tc-99m-MAA scan is also useful to demonstrate the presence of any gastrointestinal flow. As we did, it is recommended that MAA injection be performed after all vessels of concern have been embolized. The so-called single photon emission computed tomography (SPECT-CT) fusion images, the fusion of the images of SPECT after the infusion of the Tc-99m-MAA with the diagnostic CT images, allow us to better localize any suspicious foci of activity (Fig. 2). The shunting evaluation allows the physician to minimize any uncertainty in microsphere distribution at the time of treatment.

Although it was not the case in our patients, intratumoral arteriovenous shunting resulting in a significant lung shunting, particularly in bilobar HCC cases, may be taken care of by unilobar approach (10). Injection of MAA is performed and only one lobe is assessed at any one time. A repeat MAA injection is performed at a later session when the second treatment site requires treatment. It is also important to note that in patients with variant hepatic arterial anatomy the MAA can and should be fractionated in order to evaluate the entire liver in one angiography setting (10).

Embolization of extrahepatic vasculature

The identification and isolation of the hepatic vasculature are critical when performing radioembolization. One devastating complication is extrahepatic delivery of Y-90 particles, most commonly to the gastrointesti-

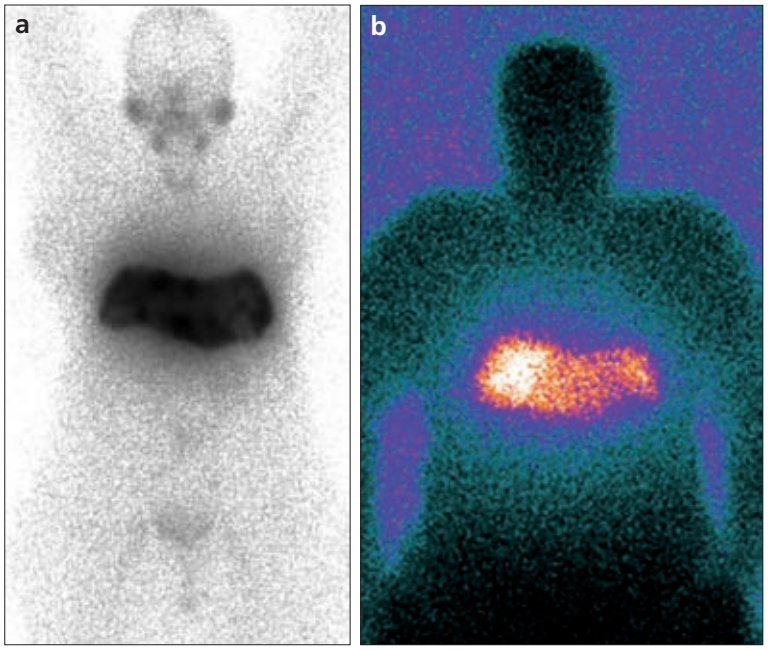

Figure 1. a, b. Gamma camera scan **(a)** after Tc-99m-MAA delivered intra-arterially suggesting that all activity is accumulated within the liver with no extra-hepatic shunting. Bremsstrahlung scan **(b)** within an hour after Y-90 microspheres delivered intra-arterially in the same patient.

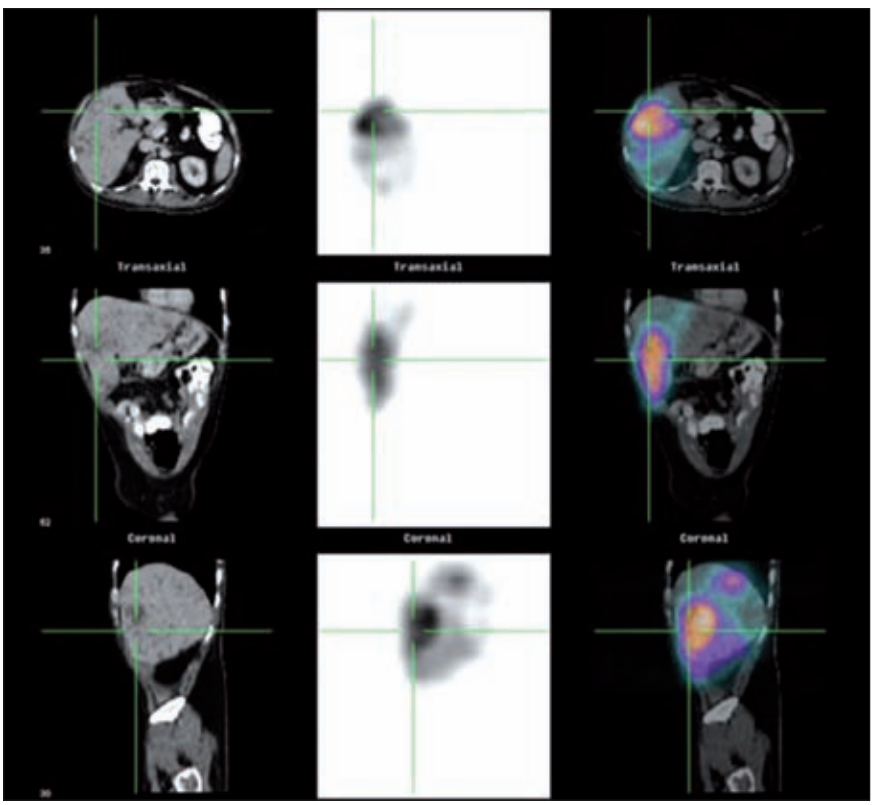

Figure 2. SPECT-CT fusion images showing the distribution of the Tc-99m-MAA in concordance to CT images which were obtained for PET-CT study.

nal tract, invariably leading to severe gastritis and possibly even ulceration (2). Although some gastric and duodenal ulcers can be treated medically, surgical intervention is sometimes required. When gastrointestinal ulceration or radiation gastritis is suspected as an adverse event, patients should undergo endoscopy for confirmation of ulceration, location of injury, and assessment of the size of the ulcer (10). As opposed to standard gastrointestinal ulcers, radioembolization-induced ulceration arises from the serosal surface, possibly decreasing the ability for the ulcer to heal or be seen using endoscopy. Hence, every effort should be made to minimize the risk of nontarget Y-90 administration.

The largest extrahepatic vessel in the area of concern is the gastroduodenal artery (GDA), which is expected to provide branches to the duodenum, pancreas, and stomach. It is recommended that the GDA be embolized routinely to protect the gastrointestinal tract from reflux of Y-90 microspheres during hepatic artery injection (Fig. 3). The next most important vessel to identify is the right gastric artery (Fig. 4). Although the origin of this vessel is variable and may arise from any site in the hepatic artery, the left hepatic artery is the most common origin of the right gastric artery. Embolization of the right gastric is also recommended to prevent catastrophic stomach ulcers. If antegrade catheterization of the right gastric artery cannot be performed, continuous anastomosis with the left gastric artery can be seen in some patients, for which retrograde catheterization can be accomplished from the left gastric artery (Fig. 5). There are many other hepatic arterial variants and accessory vessels that may interfere with the radioembolic treatment (10, 13). Extensive initial patient work-up is essential in the treatment of liver tumors with Y-90 microspheres. The falciform artery, supraduodenal artery, and cystic artery must also be identified during the initial arteriograms (Fig. 6). The blood supply to the gallbladder comes not only from the cystic artery, but also from perforators to the body of the gallbladder, the hepatic parenchyma, and the GDA (13). In the context of radioembolization, although infusion of Y-90 distal to the cystic artery is ideal, it is often not possible. Although the incidence of radiation-induced cholecystitis is very low, prophylactic embolization may be considered (10).

Imaging studies

Imaging of the patients was planned as in the literature (3). All patients were evaluated via chest, abdomen, and pelvis CT scans (magnetic resonance

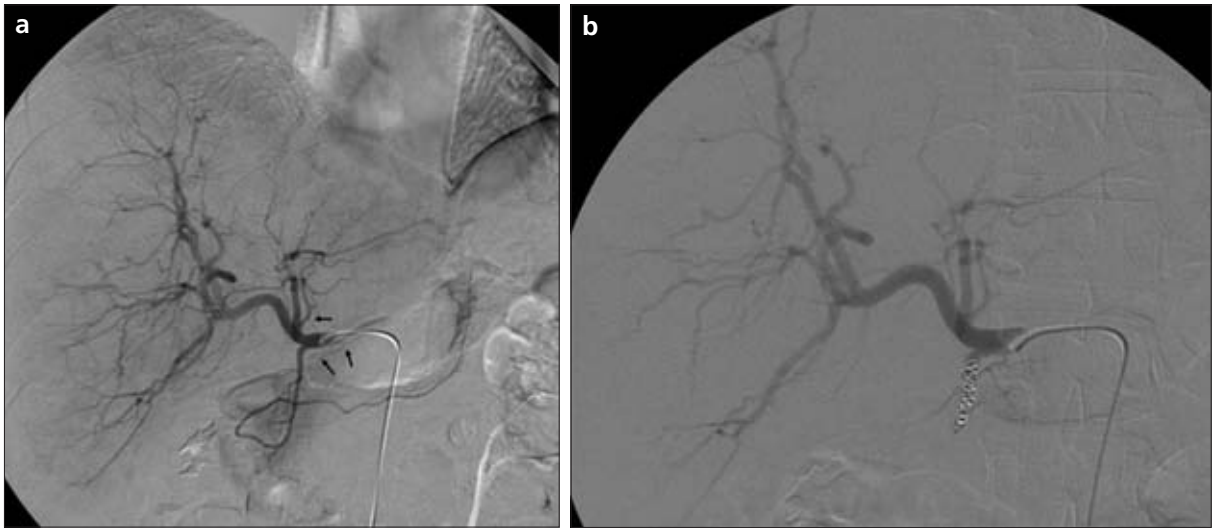

Figure 3. a, b. Common hepatic artery injection angiogram **(a)** showing standard hepatic arterial anatomy with a very short proper hepatic artery. Also note the diminutive filling of the right gastric artery **(***arrows,* **a)** off the left hepatic artery. The same injection immediately after proximal coil embolization of the gastroduodenal artery **(b)** to prevent non-target Y-90 embolization in case of reflux.

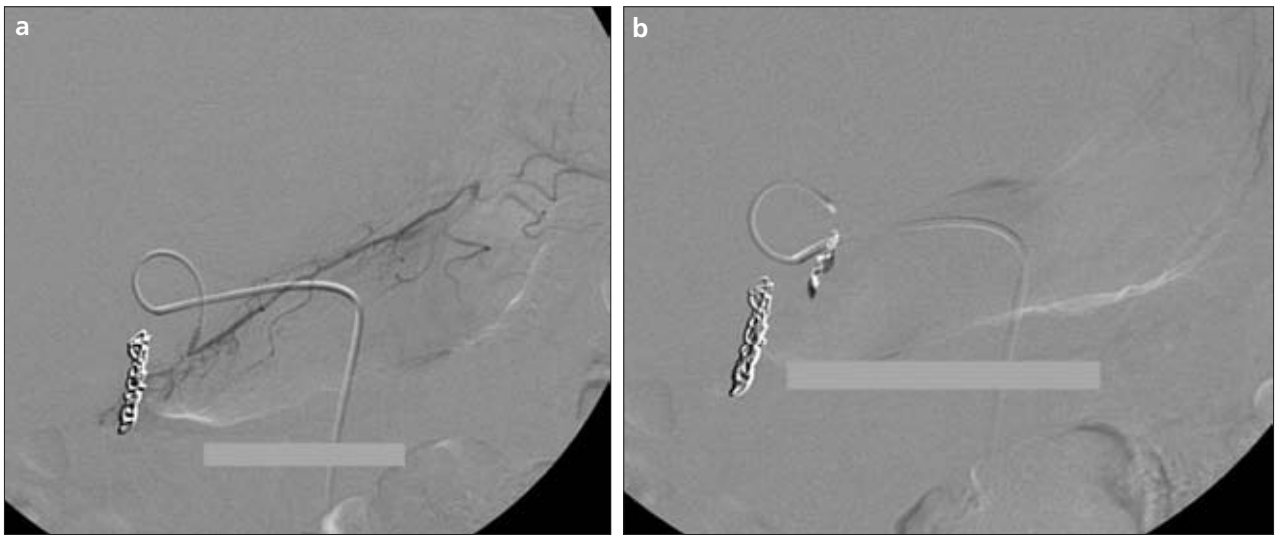

Figure 4. a, b. Superselective catheterization of the right gastric artery **(a)** off the left hepatic artery of the patient in Fig. 1. Digital subtraction angiography image right after successful deployment of the coils into the proximal part of the right gastric artery **(b)**.

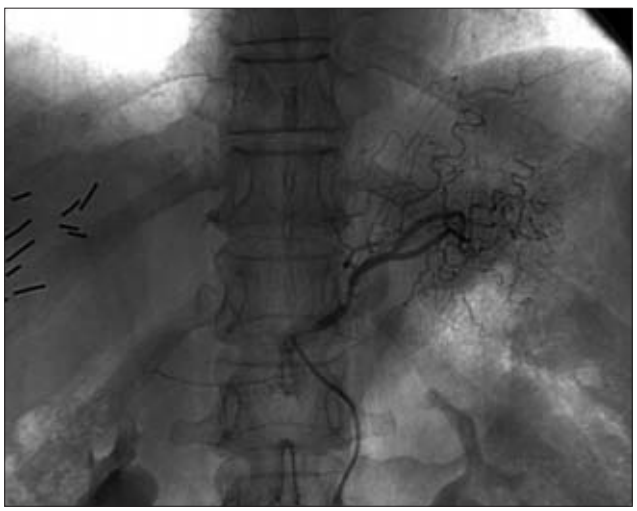

Figure 5. The retrograde right gastric artery filling by power injection from the left gastric artery.

imaging [MRI] was also used only for a few patients) to detect extrahepatic metastases and determine liver tumor location, size, and number. All scans of the abdomen were 3 phase, performed with oral and IV contrast, with a slice thickness 5 mm through the abdomen. All of our patients underwent FDG-PET-CT scanning before and after treatment. "Response evaluation criteria in solid tumors" (RECIST) were used to assess the patients before and after treatment (14).

Unlike RECIST criteria, FDG-PET-scan response criteria are not yet uniform, but were typically used to evaluate response 6–8 weeks after treatment, compared with a pretreatment scan performed

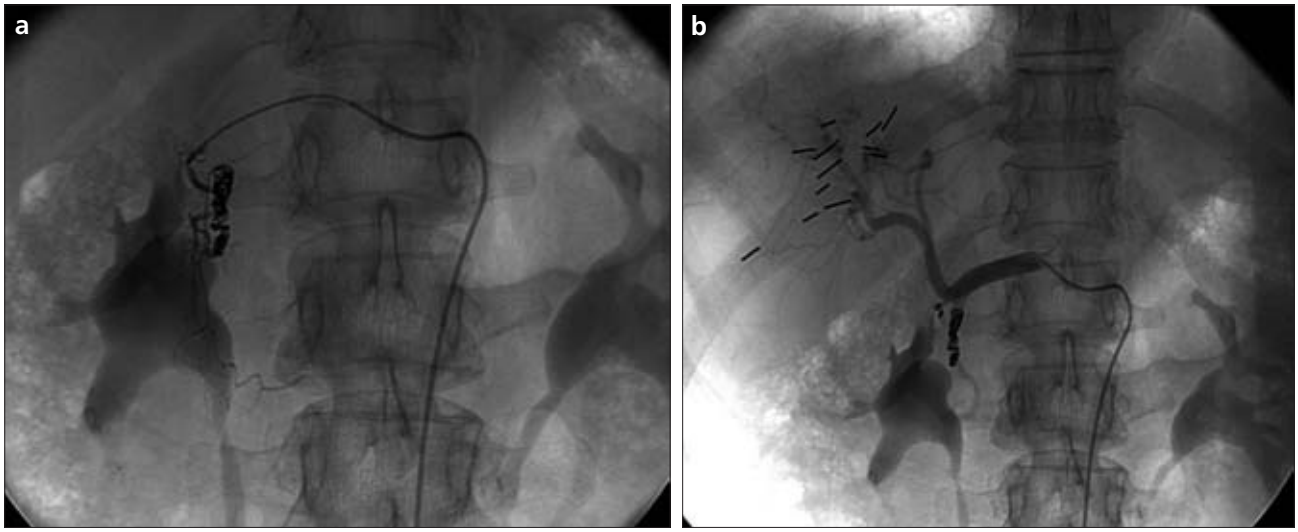

Figure 6. a, b. Superselective supraduodenal artery injection **(a)** arising off directly from the proper hepatic artery. Note the coils within the gastroduodenal artery. Common hepatic artery injection **(b)** after proximal embolization of the gastroduodenal and supraduodenal arteries.

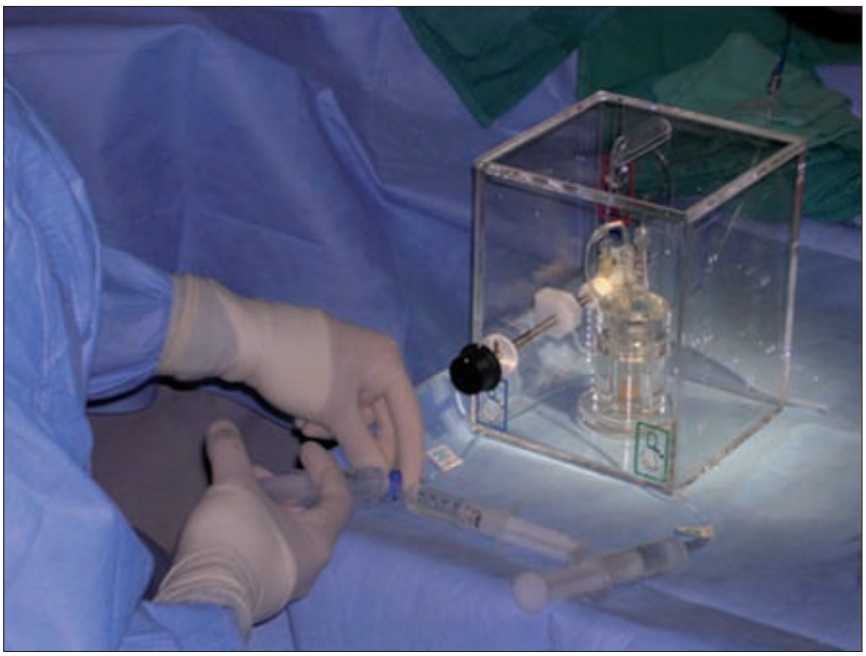

Figure 7. Plexiglass delivery box for radioembolization. After appropriate positioning of the microcatheter to the desired location of the hepatic artery, the delivery of the Y-90 loaded microspheres is done by using the syringes attached to the box as a clean (not sterile) procedure.

within 4 weeks before the treatment. FDG-PET-CT may have limitations in tumors known to have low glucose metabolism, such as HCC. However, decrease in standardized uptake value (SUV) of the known high metabolic lesions and absence of new lesions indicates good metabolic response and is a good indicator of outcome.

Radioembolization procedure

The catheter is usually positioned in essentially the same location as that used at arteriography for therapy planning. Radioactive microspheres that have the pre-calibrated activity are suspended in sterile water inside a vial that is housed in a shielded container (Fig. 7). Although it is a relatively complex delivery system, an experienced interventional radiologist can easily get used to it. A three-way stopcock allows sequential infusion of the Y-90 microspheres and contrast material injection for monitoring the progress of infusion (15). As recommended, post-procedure bremsstrahlung scans were obtained within an hour in all our patients to document that there was no extrahepatic activity on the MAA scan (Fig. 1).

Postprocedure management and follow-up

Radioembolization is generally performed on an outpatient basis in the United States. However, our patients were admitted to the hospital for close overnight observation for arterial puncture and post-embolic syndrome, as is done in many European countries. Because Y-90 microspheres are exported to our country via Australia-Germany-Turkey flight route, procedure timing has to be arranged according to the flight hours to avoid radioactive decay of Y-90, which has a half-life of 64 hours. The radioactive vial is routinely brought to our hospital at noon, which causes a delay for an outpatient transarterial procedure. Following the procedure, hemostasis was obtained by manual compression. After overnight observation at the hospital, all patients were discharged home. All patients were placed on a proton pump inhibitor (omeprazole 20 mg) for 7–10 days before and after treatment. Oral methylprednisolone therapy may be given to non-diabetic patients for the next 6 days to relieve the fatigue that ensues in most patients. Patients may receive 7–10 days of a fluoroquinolone or cefuroxime if the entire right lobe is to be treated and the cystic artery was thought to be perfused with microspheres. Tumor markers (AFP, CEA,

CA-19-9), complete blood count, liver function tests, and routine biochemical tests are obtained 4–6 weeks post-procedure. This is also the time recommended for cross-sectional (triphasic CT, dynamic gadolinium-enhanced MRI, perfusion imaging) and functional imaging (FDG-PET-CT) tests to assess the results of therapy. The opposite lobe is to be treated shortly following assessment of response and the demonstration of lack of diffuse progression. None of our patients had opposite lobe treatment in the 8-month follow-up because they had a prior hepatectomy or low tumor volume at the opposite lobe.

Results

Initial hepatic arteriography with visceral artery embolization and Tc-99m-MAA infusion prior to Y-90 treatment was performed in all patients primarily for isolation of the hepatic artery circulation and to prevent extrahepatic shunting to the lungs and gastrointestinal tract (Fig. 1a). As a result of the various hepatic arterial anatomic variations like the replaced right hepatic artery arising from the superior mesenteric artery, or previous surgical arterial ligations, coiling of arteries as potential shunts to gastrointestinal system were not needed in all patients. Besides, after having some experience with radioembolization procedure, coiling of each angiographically visible potential shunt may not be considered in every single patient depending on the hepatic arterial anatomy, target lobe to treat and the experience of the interventional radiologist. However, the gastroduodenal artery (n = 5), right gastric artery (n = 1), and supraduodenal artery (n = 1) were embolized with microcoils to prevent possible gastrointestinal shunts in our patients (Figs. 3–6). The major blood supplying vessel of hypervascular tumors was determined, and selective catheterization of the right hepatic artery (n = 7), posterior branch of the right hepatic artery (n = 1), and the left hepatic artery (n = 1) was performed. After getting familiar with the radioembolization infusion technique and treating a number of patients, we felt that the embolization of the each potential shunt (including the GDA and right gastric artery) was not necessary in every patient depending on the target lobe to treat or hepatic arterial anatomy. From our limited experience, as long as the proper hepatic artery is long enough to prevent reflux, MAA infusion can be done at a desired location for right lobe treatment, avoiding unnecessary occlusion of an important mesenteric blood supplier like the GDA (similar to the radioembolization technique from the replaced right hepatic artery taking off from the SMA). If a gastrointestinal shunt is suspected on the subsequent MAA scan, the GDA and right gastric arteries must be embolized to ensure that the most common sources of extrahepatic shunts are controlled. Because non-target embolization may lead to catastrophic complications such as gastrointestinal ulcer and perforation, it is strongly recommended that all potential extrahepatic feeders be embolized initially (before the first MAA injection) until the operator becomes really comfortable with the procedure. Of note, the GDA was surgically ligated in our one patient, in which the posterior branch of the right gastric artery was used for the final Y-90 injection. As most of the patients in this study group underwent right lobe treatment, and there was no evidence of gastric shunting at MAA scan, the right gastric artery was occluded only in 1 patient. Five mCi Tc-99m-MAA delivered intra-arterially in all patients after the embolizations were performed, and shunting was determined by SPECT-CT fusion images (Fig. 7). In the patient with pancreatic adenocarcinoma metastases, the source of the existing hepatogastric shunt could not be depicted and embolized despite the repetitive hepatic angiographies; so the Y-90 therapy was given into a segmental branch of the right hepatic artery instead of a lobar treatment. SIR-sphere radioembolization therapy could not be performed in one patient because of hepatogastric shunting, despite coil embolization of the GDA.

One of our patients developed shakes and chills immediately after the procedure, which lasted less than 1 hour. Both the onset of symptoms and their resolution were quite rapid. No medication was needed to relieve the patient's self-limiting symptoms.

Only one patient underwent two sessions of radioembolization, in which the entire residual left lobe was compromised by numerous HCC metastases. No significant hepatopulmonary shunting was determined (maximum 9% shunting). The body surface area (BSA) method was used to calculate the Y-90 dose in all patients. The mean dose of Y-90 was 1.24 GBq (range, 1.11–2 GBq). Post-procedure bremsstrahlung scans were obtained in all patients (Fig. 1b). There were no complications related to initial hepatic arteriograms or Y-90 treatment sessions. Post-procedural mild to moderate fatigue was noted for the next 7 days in all patients, with mild to moderate fever and abdominal pain in some patients (all were self-limited, with complete resolution within 4 weeks). Liver function tests during the 8-month follow-up period (range, 1–8 months) were stable in all patients. All patients had at least partial response of the target lesions at the treated liver lobes according to the RECIST criteria.

In the early follow-up at 4–6 weeks post-therapy, FDG-PET-CT showed decrease in number and metabolic activity of the lesions in the treated liver regions in all nine patients. FDG-PET-CT displayed new lesions in the non-treated liver segments in three patients and new extrahepatic foci in four patients. One patient with colorectal cancer died of disease recurrence, which caused multisystem failure, approximately 6 months after Y-90 microsphere therapy. All other patients are alive and being followed up with regressed/ stable disease of the treated lobes as of January 2009.

Discussion

Radioembolization, a form of intra-arterial brachytherapy, is a technique in which particles of glass or resin, impregnated with the isotope Y-90, are infused through a catheter directly into the hepatic arteries. Y-90 is a pure β emitter and decays to stable Zr-90 with a physical half-life of 64.1 h. The average energy of the β particles is 0.9367 MeV, has a mean tissue penetration of 2.5 mm, and has a maximum penetration of 10 mm. There are currently two commercially available agents: SIR-Spheres and TheraSphere. SIR-Spheres are resin-based particles, approximately 29–35 nm in diameter, in which the Y-90 and resin are intimately bound. The standard activity vial is 3 GBq, of which a predetermined amount is decanted in the nuclear medicine pharmacy from the vial for injection into the patient. A 3-GBq activity vial contains between 40

million and 80 million microspheres. Each microsphere contains 50 Bq of activity at the time of calibration (11). Radioembolization refers to the use of TheraSphere, SIR-Spheres, or other microsphere agents that have the emission of radiation as their primary and microembolization as their secondary modes of action (10).

Radioembolization, as a kind of brachytherapy, has a different treatment mechanism from embolization. Microspheres laden with the β-emitting isotope Y-90 are used; they are small enough to pass deep into the tumor vasculature but too large to pass through the capillary bed and reach venous circulation, preventing deposition in the lungs (4). On the other hand, fluoroscopic guidance, angiographic end points of embolization and stasis, and the need to modify this based on angiographic findings make this treatment a true embolization procedure. There is a spectrum of radioembolic effects that exists with this therapy: with TheraSphere, there is high specific activity and a small number of microspheres (mild radioembolic effect); with SIR-Spheres, there is low specific activity and a large number of microspheres (moderate/high radioembolic effect) (10). It is this varying number of microspheres, embolic effect, and possible vascular saturation that makes fluoroscopic observation necessary. Comparing the two commercially available Y-90 microspheres, Sato et al. reported no identifiable change in angiography after treatment, based on blinded review of before and after glass microsphere radioembolization (5). Conversely, stasis of hepatic arterial flow represents the major reason for stopping delivery of resin microspheres before the full planned activity has been given. Stasis is not desired, in part, because of the shunting of microspheres into the normal liver, creating tumor hypoxia (5). Because of their higher embolic potential, SIR-Spheres are contraindicated in the setting of complete portal vein thrombosis, as the number of particles in a typical vial may result in embolic occlusion of the patent vessel. Hence, if SIR-Spheres are to be used in the setting of portal vein thrombosis, dose fractionation should be considered (10).

Although there are different methods for calculating activity in Y-90 microspheres, those most frequently used are the empiric method and the BSA method (4). The BSA method was proposed to account for body and liver size differences and was the preferred method for dose calculation in our patients. BSA and the percentage of tumor to the liver (TLR, tumor liver ratio) values were used (dose of Y-90 = BSA – 0.2 + TLR) in our study (16).

Although much of the early clinical experience with Y-90 involved whole-liver infusion, this treatment paradigm is no longer recommended. Enhancements in microcatheter technology have decreased the use of surgically implanted pumps for the treatment of liver tumors. Furthermore, there exists significant extrahepatic flow, described throughout this article, through small vessels that can only be avoided using lobar/segmental infusions. For radioembolization, a treatment paradigm that parallels TACE is recommended, i.e., lobar or subsegmental infusions (10).

Percutaneous interventions have been widely used in the treatment of liver tumors worldwide. Radiofrequency ablation, cryoablation, and percutaneous ethanol ablation have been shown to be effective for the treatment of small liver tumors (10, 17). Similarly, liver-directed transarterial techniques, such as TACE and transcatheter arterial bland embolization, have shown clinical benefit in selected patients (18).

It has been shown that the TACE procedure itself is a safe and efficient procedure when selection criteria are applied strictly, particularly in terms of liver function tests. Although the same patient selection criteria are applied for radioembolization, it appears that radioembolization may be undertaken in the setting of abnormal/elevated liver function if a segmental infusion can be performed, without significant impact on liver functions (19). This is a critical assumption, depending on the fact that the transarterial treatments are generally applied after several chemotherapy regimens, which usually compromise the liver functions because of toxicity. Applying radioembolization as a first-line treatment in select patients with widespread liver disease may act like radiofrequency ablation in the setting of relatively limited disease. Multicenter randomized controlled studies are warranted to determine the actual role of radioembolization in liver tumor therapy algorithm. Several clinical studies of this therapy in different tumor types has shown promising results in metastatic disease from colorectal cancer (3, 6), hepatoma (20), neuroendocrine tumors (21), breast cancer (22), and other tumor types (4).

External radiotherapy at doses above 50 Gy is effective in destroying colorectal tumors. The limitation in this treatment is the tolerance of normal liver parenchyma to radiation; the maximum acceptable dose of 35 Gy for the whole liver is far below that required to destroy adenocarcinoma metastases, estimated at 70 Gy or more. Microsphere implantation within the tumor while sparing the adjacent normal liver is the key to its importance: liver tolerance to microsphere therapy is excellent, although tumor destruction, even in large tumors, is observed. The actual dose given to each lobe or segment, or to the whole liver, is dependent upon the tumor vasculature capacity. Both the embolic-related and the radiation-related edema effects in the liver and the intensity of liver radiation during this time are stressful on the body and counteracted by a short burst of steroid therapy (3). The results of a study of 208 patients with colorectal cancer showed that CT partial response of 35%, positron emission tomography response of 91%, and reduction in carcinoembryonic antigen of 70% were achieved (3). Combining the newest and most effective chemotherapy agents for colorectal cancer with microspheres is the logical next step, now that the effectiveness and safety have been established in microsphere-alone–treated patients (3).

Neuroendocrine tumors are an uncommon, heterogeneous group of different slow growing, hormone-secreting malignancies. Transcatheter bland embolization and TACE are known to be effective treatment options in the palliation of neuroendocrine tumors, particularly for symptom-free survival (23). Internal radiotherapy has also being used to control, eradicate, or simply debulk hepatic metastases, often to palliate carcinoid syndrome or local pain from liver capsular stretching. Selective uptake by carcinoid tumors provides the proximity needed for β radiation cell killing (21).

HCC, as the most common primary tumor of the liver, is chemotherapy resistant, and—because of low liver reserve in most patients and compromised portal vein flow in approximately 25%—unresectable HCC has

a dismal prognosis. Tumor burden in the liver is a major threat to patient survival and well-being; and because systemic chemotherapy is ineffective, local liver-directed therapies including hepatic arterial therapies have been developed to reduce tumor burden, providing palliation and the potential for increased survival. Y-90 microsphere treatment appears to be well tolerated and can be used safely in carefully selected patients (7).

Idiosyncratic reaction has also been described immediately after radioembolization, which is very similar to that of urokinase (10). Although it is reported to be a rare and unusual reaction, radioembolization with Y-90 may cause a short-lived idiosyncratic reaction with symptoms of shakes, chills, and alterations in hemodynamics and vital signs. Contrast material reaction should be included in the differential diagnosis. As with urokinase reaction, management is supportive, including fluids if hypotensive, as well as antihistaminic medications. Although it is difficult to predict which patients will have this reaction, it has been seen commonly in patients with arterioportal shunting who undergo radioembolization (10).

Patient selection, tumor response, treatment techniques, and complications including acute and late onset radiation toxicity have been reported in the literature. Radiation-induced liver disease (RILD) was initially described as radiation hepatitis after external beam radiation and is widely acknowledged to be a clinical entity that can present with ascites 2 weeks to 4 months after hepatic radiation (24). RILD is now known to be a result of veno-occlusive disease rather than hepatitis. RILD seems to be the most severe toxicity of microspheres, but there is no identified relationship between toxicity and tumor type (4). Clinically, patients develop rapid weight gain, increased abdominal girth, liver enlargement, jaundice, and increased liver enzymes, particularly alkaline phosphatase, occurring before 90 days post-treatment (4, 25). Most of these patients survive RILD but may require aggressive vascular intervention or therapy to control symptoms from abdominal ascites, including transjugular portosystemic shunt. Furthermore, it is now believed that the incidence of RILD might be higher than was initially thought with commonly accepted doses of radioembolization, which lead up to 20% off the calculated dose in current practice. High doses of corticosteroids traditionally are administered in an attempt to decrease intrahepatic inflammation. Treatment results are variable and mostly unsuccessful, as the condition progresses in some patients to hepatic insufficiency of various degrees (15). For enhanced patient safety, the dose calculation and patient selection must be done carefully.

Non-standard chemotherapeutic release and local concentrations delivered by conventional TACE techniques have mostly been replaced by drug-eluting beads, which have predictable pharmacokinetics and can achieve higher doses of the chemotherapeutic agent and prolonged contact time with cancer cells (26). However, systemic effects of locally given chemotherapy are unavoidable in TACE. When comparing radioembolization with TACE, radioembolization has less systemic toxicity and can be done as an outpatient procedure, making it attractive to both patients and physicians. Post-embolic syndrome is usually milder after radioembolization than after chemoembolization. Another key point is the PET-CT monitoring of the treatment response. Although the cost increases significantly with numerous PET-CT scans, it allows clearer evaluation of the metabolic responses with unclear survival contribution.

From our limited experience, the radioembolization procedure promises to be a first-line treatment in unresectable liver cancer. However, there is a need for randomized controlled multicenter studies to document cost-effectiveness. Technical aspects of radioembolization are almost entirely an interventional radiology procedure. However, because oncology patients should always be evaluated in a multidisciplinary fashion for the maximal benefit for the patient, radioembolization should be implemented to the treatment algorithms of hospital dynamics. Institutional policies, hospital radiation safety committees, interventional radiologists, oncologists, general surgeons, and nuclear medicine physicians should function in a collegial manner. Because of the relatively short history of radioembolization and the lack of evidence on cost-effectiveness, careful steps should be taken in parallel to the studies published in the literature.

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