
Hepatic Radioembolization with Yttrium-90 Containing Glass Microspheres: Preliminary Results and Clinical Follow-Up

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The treatment of hepatic tumors remains unsatisfactory. These lesions receive most of their blood supply from the hepatic artery, therefore the hepatic artery administration of beta-emitting particulate radiopharmaceuticals is an attractive approach to deliver therapeutic irradiation to the liver and differentially to tumors within the liver. **Methods:** A Phase I dose escalation study of the hepatic tolerance to radiation delivered by ^{90}Y containing glass microspheres was carried out in 24 patients with hepatic malignancy. Doses of ^{90}Y microspheres to achieve an estimated whole-liver nominal absorbed radiation dose of 5000 cGy (two patients), 7500 cGy (six patients), 10,000 cGy (seven patients), 12,500 cGy (six patients), and 15,000 cGy (three patients) were administered via the hepatic artery. The administered nominal absorbed radiation dose (NARD) was estimated based on liver volume determined from CT scans and the assumption of uniform distribution of microspheres throughout the liver. **Results:** No hematologic, hepatic or pulmonary toxicity was encountered in the dose range examined during a mean follow-up period of up to 53 mo. Reversible gastritis or duodenitis was encountered in four patients without imaging or biopsy evidence for extra-hepatic deposition of microspheres. Response data, based on CT scans obtained 16 wk after treatment, showed progressive disease in eight patients, stable disease in seven patients, minimal response in four patients and partial response in five patients. Subsequent follow-up revealed three long-term survivors at 204, 216 and 228 wk. **Conclusions:** These preliminary data demonstrate that in the examined dose range, radiation may be safely delivered to liver tumors by means of ^{90}Y glass microspheres with encouraging response data.

Key Words: yttrium-90 glass microspheres; hepatic tumors; hepatic metastases; hepatic artery delivery; therapeutic radiopharmaceutical; radioembolic therapy

J Nucl Med 1994; 35:1637-1644

The relatively greater arteriolar density in hepatic tumors, both primary and metastatic, compared to the surrounding normal liver, makes the hepatic arterial administration of microspheres labeled with an appropriate radioisotope an attractive therapeutic option. The deposition of microspheres in proportion to arterial flow could result in approximately a threefold or greater radiation exposure in tumor nodules relative to normal liver, even in tumors classified as hypovascular by angiography, such as metastatic colorectal carcinoma (1).

Prior attempts at hepatic radioembolization therapy employed resin or ceramic microspheres labeled with yttrium-90 (^{90}Y) with promising initial results. Yttrium-90 is a pure beta particle emitter with a physical half-life of 64 hr and a mean energy per disintegration of 0.937 MeV. The beta particles have a mean tissue penetrance of 2.5 mm, with a maximum of about 10 mm. These physical characteristics make ^{90}Y an almost ideal isotope for localized internal radiation therapy. Limitations in early studies included an inability to accurately calculate the delivered dose, and the inability to monitor regional perfusion, leading to excessive gastrointestinal toxicity. Also, leaching of ^{90}Y from the spheres resulted in myelosuppression and excessive shunting of particles through the liver caused pulmonary fibrosis in several cases (2-4).

A new radiopharmaceutical (TheraSphere, Theragenics Corp., Atlanta, GA) has recently entered clinical trials. This agent consists of a 22- μ glass sphere in which inert ^{89}Y is incorporated into the glass matrix. Prior to patient use, neutron bombardment is employed which converts the inert ^{89}Y to radioactive ^{90}Y . As it is part of the glass matrix, the ^{90}Y cannot leach under physiologic conditions (5). The agent is supplied sterile and pyrogen-free in a lucite, vee-bottom vial, with the dose calibrated for each patient.

The primary purpose of this Phase I dose escalation trial is to evaluate the hepatic tolerance to radiation delivered by ^{90}Y microspheres up to a whole-liver nominal absorbed radiation dose of 15,000 cGy, and to evaluate the ability, using modern angiographic techniques and scintigraphic monitoring, to safely deliver therapeutic radioactive micro-

Received Jul. 6, 1993; revision accepted Jan. 20, 1994.

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spheres to the liver without excessive shunting through the liver to the lungs or delivery to the gut.

PATIENTS AND METHODS

The eligibility criteria, pertaining to our protocol and that adopted by others, have been previously described (6,7). Briefly, patients with primary hepatobiliary tumors, or colorectal or neuroendocrine tumors metastatic to the liver were considered for this study. Patients must have failed conventional therapy and have satisfactory hematologic, hepatic and renal function as defined by a total leukocyte count $>4,000/\text{mm}^3$, a granulocyte count $>2,000/\text{mm}^3$, a platelet count $>150,000/\text{mm}^3$, serum albumin >2.5 gm/dl, bilirubin <2 mg/dl, serum glutamate-oxalate transaminase less than 6 times normal, prothrombin time within 3 sec of control (or correctable with vitamin K), and a serum creatinine <2 mg/dl. Patients who had received prior hepatic radiation therapy were ineligible. Prior to entering the study all patients gave written informed consent as approved by the institutional review board for experimental studies in humans.

There were 15 males and 9 females, ages 22 to 79 yr in this study. Seventeen patients had metastatic colorectal carcinoma, six had metastatic neuroendocrine tumors and one had a primary hepatocellular carcinoma. All patients had been heavily pretreated with either systemic 5 fluorouracil, hepatic arterial floxuridine or a combination of these therapies, and had CT evidence for progressive hepatic disease.

Pretreatment Investigations and Angiographic Manipulations

Pretreatment evaluation consisted of a complete history and physical examination, chest radiograph, sulfur colloid liver-spleen scan and abdominal CT. Laboratory evaluation included a complete blood count, BUN, creatinine, SGOT, SGPT, alkaline phosphatase, LDH, bilirubin, prothrombin time and tumor markers (when indicated).

Angiography was performed 4–6 wk prior to ^{90}Y therapy to determine whether the hepatic arterial anatomy and the hemodynamics of the hepatic circulation would allow for administration of ^{90}Y microspheres as required by the protocol. In those patients where baseline vascular anatomy and flow were unsatisfactory (i.e., not permitting microspheres to be confined to the liver), aberrant hepatic arteries were occluded during this initial examination using stainless steel coils for hepatic arterial redistribution (8). In three patients, this baseline angiography demonstrated such aberrant hepatic artery branches (replaced right hepatic artery, replaced left hepatic artery and accessory left hepatic artery in one case each) which were then successfully occluded. Arteriograms performed immediately after the embolization demonstrated complete reconstitution of the aberrant hepatic artery by way of intrahepatic collaterals.

Dose Calculation

Hepatic volumes were calculated from 10-mm thick contiguous CT slices by manually tracing the liver outline, and assuming the total volume equalled the sum of the volumes of all slices. Care was taken to obtain each CT slice in the same phase of respiration. The patients were all cooperative and not acutely ill at the time of CT. Each was carefully coached to hold their breath in the same degree of comfortable full inspiration during scanning. The required activity of ^{90}Y necessary to achieve the desired nominal liver radiation exposure was calculated with the following formula (6):

Microsphere dose (MBq)

$$= \frac{\text{Radiation exposure (cGy)} \times \text{Liver mass (kg)}}{5}$$

Microsphere dose (mCi)

$$= \frac{\text{Radiation exposure (rads)} \times \text{Liver mass (kg)}}{182}$$

This assumes uniform distribution of the microspheres throughout the liver, and complete decay in situ of the ^{90}Y . The desired nominal radiation dose was 5000 cGy (two patients), 7500 cGy (six patients), 10,000 cGy (seven patients), 12,500 cGy (six patients) and 15,000 cGy (three patients). The liver volume, administered activity, calculated nominal radiation dose and desired nominal radiation dose for each patient are summarized in Table 1.

Hepatic Radioembolization

All patients were housed in the Clinical Research Center where specialized nursing care was available prior to and after hepatic radioembolization.

The femoral approach was used for all percutaneous hepatic arterial catheterizations. In patients with normal hepatic arterial hemodynamics (antegrade flow in the gastroduodenal and right gastric arteries) a 6 French balloon occlusion catheter (Medi Tech, Watertown, MA) was selectively placed in the distal common hepatic artery and the balloon inflated (9). In each patient, hepatic perfusion was examined with digital subtraction arteriograms (DSA) at injection rates from 0.5 to 4 ml per second. It was determined that an infusion rate of 1.0 ml per second resulted in perfusion to the entire liver without reflux into the gastroduodenal or right gastric arteries which would lead to extrahepatic deposition of microspheres (Fig. 1). This rate was used in all patients. This approach is similar in concept to the optimization of infusion rates for hepatic artery chemotherapy (10).

In patients without extrahepatic branches of the hepatic artery (prior surgery), or in patients with celiac or common hepatic artery stenosis (where reversed flow is already present in extrahepatic arterial branches) either a standard 5 French angiographic catheter, or a 3 French teflon catheter used coaxially was employed.

After the catheter was in satisfactory position, it was fixed at the puncture site and the patient was transported to the nuclear medicine suite for microsphere administration. Catheter patency was maintained with a constant infusion of normal saline with heparin, 10 unit/ml, infused at 20 ml/hr.

Microsphere Administration

Prior to ^{90}Y administration, the regional perfusion by the catheter, and an estimate of the A-V shunting across the liver was made with radionuclide angiography, as previously described (11). Briefly, 6 mCi (222 MBq) of $^{99\text{m}}\text{Tc}$ -MAA was infused via the arterial catheter at 1 ml/sec (the rate determined from DSA). Anterior, posterior and both lateral views of the upper abdomen were obtained, followed by SPECT imaging. The anterior and left lateral views were repeated after the patient ingested CO_2 -producing granules (Easy-Gas) to distend the stomach and assist in the detection of extrahepatic perfusion (12–14). The abdominal images were compared to the previously obtained $^{99\text{m}}\text{Tc}$ -sulfur colloid liver spleen scan and examined for the presence of extrahepatic perfusion, and extent of hepatic perfusion. The presence of

TABLE 1
Therapy Data

Patient dose (cGy)	Liver volume (cc)	Administered (mCi)	Calculated nominal absorbed radiation dose (cGy)*	Prescribed nominal absorbed radiation dose (cGy)*	Ratio of tumor-to-liver distribution of ^{90m} Tc-MAA (mean ± s.d. (n))
1	1606	47	5500	5000	3.71 ± 3.21 (3)
2	1552	47	5700	5000	1.77 ± 0.39 (4)
3	1490	59	7400	7500	2.57 ± 0.51 (3)
4	1968	92	8600	7500	2.51 ± 1.31 (3)
5	2450	115	8700	7500	4.14 ± 1.85 (3)
6	3441	150	8100	7500	1.77 ± 0.58 (4)
7	3141	145	8500	7500	1.85 ± 0.38 (4)
8	3298	148	8300	7500	1.96 ± 0.05 (2)
9	1709	117	12700	10000	3.77 ± 2.48 (3)
10	1954	117	11100	10000	4.52 ± 3.36 (4)
11	1494	111	13800	10000	1.72 ± 0.58 (4)
12	2668	202	14000	10000	4.44 ± 2.58 (4)
13	1928	107	10300	10000	LD†
14	1851	107	10700	10000	LD†
15	1637	95	10700	10000	3.80 ± 2.13 (4)
16	2535	172	12500	12500	1.93 ± 0.64 (4)
17	3367	228	12500	12500	4.08 ± 2.13 (5)
18	2683	182	12500	12500	2.61 ± 1.35 (4)
19	1488	110	13600	12500	2.45 ± 0.18 (2)
20	1372	106	14200	12500	1.85 ± 0.33 (4)
21	1722	104	11100	12500	2.05 ± 0.51 (4)
22	1388	113	15000	15000	2.62 ± 1.38 (5)
23	1305	108	15300	15000	3.56 ± 2.52 (3)
24	1833	136	13700	15000	3.29 ± 0.94 (2)

*Nominal absorbed radiation doses assume uniform distribution of ⁹⁰Y.

†LD is quantitative data lost due to computer malfunction but qualitatively good lesion-to-liver ratio.

any detectable extrahepatic perfusion, or perfusion of less than 90% of the liver made the patient ineligible for treatment.

Images of the abdomen and chest were also obtained quantitatively to allow calculation of the lung shunt, or the fraction of the MAA which reached the lungs by way of A-V shunting through the liver. It was assumed that MAA accurately predicts the distribution of ⁹⁰Y microspheres. In the current protocol, if the lung shunt fraction would result in > 10 mCi (370 MBq) of ⁹⁰Y reaching the lungs the patient could not be treated.

The differential delivery of ^{99m}Tc-MAA to tumors and adjacent normal liver tissue was determined from profiles drawn through representative lesions depicted by SPECT (2-5 lesions per patient) (12-14).

Using a medium- or high-energy collimator, and an energy window setting of 240-440 keV, bremsstrahlung scans were obtained in the same projections as the MAA perfusion scan to document deposition of ⁹⁰Y microspheres.

Post-Treatment Evaluation

Post-therapy follow-up consisted of physical examination and laboratory studies (CBC and liver function tests) weekly for 8 wk, then every 8 wk until disease progression. Response to therapy was followed with abdominal computed tomography every 8 wk until disease progression. A partial response, or progressive disease was defined using standard oncological criteria as a 50% change in the product of the greatest diameters of a given lesion on sequential scans. Chest radiographs were also obtained every 8

wk until disease progression. Patients were removed from the protocol at the time of disease progression and returned to their referring physicians for subsequent care and follow-up. These physicians communicated any development of respiratory disorders, hepatic failure not due to metastatic progression and date of death to the investigators. The referring physicians followed up the patients with clinical examinations and abdominal computed tomography as clinically indicated until death (up to 4 yr). The time from ⁹⁰Y microsphere therapy until progression and until death were plotted as Kaplan-Meier curves (15).

RESULTS

Two patients had functioning surgically implanted hepatic artery catheters which were used for microsphere administration. The remaining 22 patients were treated using a balloon occlusion catheter in the common hepatic artery (16 patients), a standard angiographic catheter placed in the proper hepatic artery (3 patients), a 3 French teflon catheter placed coaxially into the proper hepatic artery (2 patients), or a tapered 2.2-3 French catheter (Tracker 18, Target Therapeutics, San Jose, CA, one patient), placed coaxially into the proper hepatic artery. In two patients where a balloon occlusion catheter was used, extrahepatic branches (retroduodenal artery and an omental adhesion to the right lobe of the liver in one patient

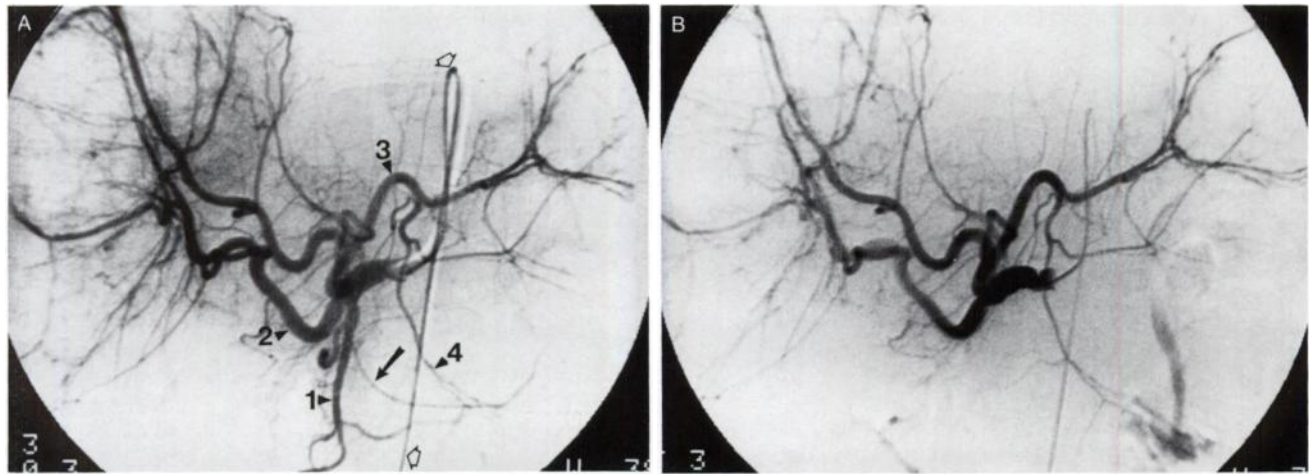


FIGURE 1. (A) Common hepatic arteriogram before balloon inflation. Note the common hepatic artery divides directly into the gastroduodenal (1), right (2), left hepatic (3), and left hepatic branch (4) arteries. The gastroduodenal and right gastric (arrow) arteries are opacified indicating antegrade flow. The catheter is identified by open arrows. (B) Common hepatic arteriogram after balloon inflation. Perfusion is now limited to the liver due to reversal of flow in the gastroduodenal and right gastric arteries (note enlarged left lobe due to diffuse metastasis).

each) were opacified at an infusion rate of 1.0 ml/sec despite the inflated balloon. In these two patients, a Tracker 18 catheter was advanced through the balloon catheter, the extrahepatic branches selectively catheterized and occluded with platinum microcoils (Hilal Coils, Cook Inc., Bloomington, IN). This angiographic technique resulted in complete hepatic perfusion without detectable extrahepatic perfusion in all cases. No angiographic complications were encountered.

Other than mild, transient elevations in the transaminase levels, no hepatic or hematologic toxicity was encountered. Fever $>101.5^{\circ}\text{F}$ was noted in four patients within 24 hr after therapy. Fatigue was reported by 18 of 24 patients. In four patients, grade 2 gastrointestinal toxicity (gastritis responding to medical management) was noted. Two of these patients had pre-existing underlying gastritis or duodenal ulcer disease diagnosed prior to ^{90}Y therapy. Endoscopy and biopsy in these patients failed to demonstrate microspheres reaching the stomach or duodenum. The endoscopic features of the gastritis were nonspecific and did not show a geographic pattern to suggest microsphere embolization. While only the mucosa was sampled at biopsy, no microspheres could be identified on histological examination. The highly refractile microspheres are readily detected and instantly recognizable on light microscopy.

The mean (\pm s.d.) ratio of $^{99\text{m}}\text{Tc}$ -MAA delivery to liver tumors relative to normal liver tissue was 2.86 ± 1.75 (mean \pm s.d.) (range 1.17–8.83) (See Table 1). It can be inferred from these data that the actual radiation dose delivered to the tumors was greater than the nominal absorbed radiation dose by approximately this factor.

The lung shut measured from 1.5% to 5.5% (mean 3.6%). Assuming the distribution of $^{99\text{m}}\text{Tc}$ -MAA accurately predicts the behavior of the ^{90}Y microspheres, this resulted in calculated pulmonary exposure of 166–1745 cGy (mean

845 cGy). During a follow-up period of up to 53 mo, no radiographic changes suggestive of pulmonary fibrosis have been observed, and no patient has developed pulmonary symptoms or signs (cough, dyspnea, dyspnea on effort, hemoptysis, sputum, pleuritic pain, cyanosis, clubbing, rales or pleuritic rubs). In no instance did symptoms or signs of pulmonary fibrosis occur during the subsequent clinical course of any patient. All physicians participating in the care of these patients were instructed to specifically seek respiratory abnormalities.

Based on the CT scans obtained 16 wk after therapy, a partial response was seen in five patients, minimal response in four patients, stable disease in seven patients and progressive disease in eight patients. Response data for the 17 patients with metastatic colorectal carcinoma were partial response (five patients), minimal response (one patient), stable disease (four patients) and progressive disease (seven patients). Of the patients with neuroendocrine tumors there were three minimal responses and three with stable disease. The patient with hepatoma had no response to therapy. The sites of progression were in the lungs in five patients, bone in two patients, lymph nodes in one patient and liver in the remaining patients. Although the median survival for such a heterogeneous group of patients is of limited significance, it is interesting to note that four of the six patients with neuroendocrine tumors survived with stable disease for a mean of 16 mo after therapy, and the median survival for patients with metastatic colorectal carcinoma was approximately 60 wk. Although this was not a study aimed at determining the therapeutic activity of the agent, tumor shrinkage at the range of doses applied indicates a degree of potential efficacy is likely to pertain. These data suggest that even at doses well below dose-limiting toxicity, some therapeutic effect was achieved.

DISCUSSION

These data demonstrate that the hepatic tolerance to radiation delivered by means of ^{90}Y containing microspheres is excellent at least to nominal absorbed radiation doses of 15,000 cGy to the whole liver. This is in keeping with the findings of others (16). This dosimetric approach assumes uniform distribution of the microspheres throughout the liver and was the one accepted by the FDA for the purposes of dose escalation. This is consistent with our preclinical studies, in which whole-liver radiation doses in excess of 30,000 cGy were compatible with survival in dogs (17). In order to optimize chances to demonstrate efficacy, dose escalation in humans to the maximum tolerated dose should be identified before full-scale phase II efficacy trials are initiated. This dose for humans may be in excess of 20,000 cGy as no dose-related toxicity was observed up to the 15,000 cGy level.

It is generally believed that the maximum dose which may be delivered to the liver by external-beam radiotherapy, without excessive risk of radiation hepatitis is between 3000 and 3500 cGy (18,19). The design of external-beam radiotherapy fields has become highly sophisticated and the radiation dosimetry can be calculated with considerable accuracy.

In contrast, the accurate determination of absorbed radiation doses from the internal administration of radiopharmaceuticals remains a major problem in nuclear medicine which at the current time is, at best, only subject to partial solution (20,21). The dose calculation for the nominal absorbed radiation dose used in the current study on which the dose escalation was based assumed the microspheres to be evenly distributed throughout the entire liver. However, a basic assumption on which the intra-arterial therapy of liver tumors rests is that arterial perfusion to tumors is greater than to normal liver. Indeed arterial perfusion to the liver tumors was demonstrated to be approximately three times that of the surrounding normal liver which is in keeping with previous experience (1). The goal of this therapy is to deliver radiation to the liver without irradiation of adjacent structures and to more selectively deliver radiation to liver tumors by taking advantage of the differential arteriolar density. The nominal absorbed radiation dose calculation clearly underestimates the true radiation dose delivered to tumors and overestimates the true radiation dose delivered to the normal liver.

While the nominal absorbed radiation dose (based on an assumption of uniform ^{90}Y distribution) represents a crude first approximation to the true radiation dosimetry, a somewhat more accurate second order approximation may be made using the mean tumor-to-normal liver perfusion ratios derived from SPECT studies of $^{99\text{m}}\text{Tc}$ -MAA distribution. Thus the tumor radiation dose would be greater than the nominal absorbed radiation dose by this ratio (valid if tumor composes a relatively small fraction of the liver volume). A yet more accurate third order approximation would require knowledge of the total liver volume occu-

ried by tumor and the perfusion ratio. Still greater accuracy could be achieved if the volume of each tumor deposit was known and could be related to the perfusion ratio for that tumor.

These approaches still fail to take into account the problems of microdosimetric inhomogeneity due to nonuniformity of microsphere distribution at a microvascular level (21,22). Despite these shortcomings, it is clear that the selective hepatic artery delivery of ^{90}Y glass microspheres will permit the specific delivery of many thousands more of cGy to the liver than is possible by external-beam radiotherapy. Within the liver there is a clear differential delivery advantage to the tumor deposits relative to normal liver which cannot be achieved by external-beam radiotherapy. Furthermore, there is no significant radiation exposure to the body wall, spinal cord, heart and pericardium, pleura, gut or pancreas as may be the case with external-beam radiotherapy.

The only organ other than the liver which is significantly irradiated is the lung which is the site of deposition for the small fraction of particles shunted through the liver. It is encouraging that in a recent report it was demonstrated that the tolerance of normal human liver to beta particle radiation delivered by ^{90}Y is in excess of 8000 cGy, which only leads to mild periportal and central venous fibrosis (16). The delivery of radiation doses by internally administered radiopharmaceutical represents an extreme form of continuous dose fractionation in which the biological effect of a given radiation dose may differ greatly from that of an equal radiation dose delivered by external-beam radiation fractionated in the usual fashion (21).

Our initial experience is not dissimilar to the results previously reported with this radiopharmaceutical in which doses of microspheres achieving whole-liver doses up to 10,000 cGy were well tolerated, without evidence for significant hepatic toxicity (6,7,22). While CT demonstrated irregular geographic low-attenuation areas in the hepatic parenchyme of 12 of 23 patients which were most pronounced 8 wk after radioembolic therapy, these had resolved by 16–24 wk without significant derangement in hepatic function or long-term clinical sequelae (24). These changes were thought to result from both microembolization and irradiation of the hepatic parenchyme and further support the concept that this tissue is highly tolerant to such injury (24). In a recent report, partial responses were seen in 9 of 53 patients, with a mean survival of 9.7 mo for the patients with colorectal cancer (23). However, the angiographic technique employed in these series may limit the efficacy of this therapy.

In one report, selective infusion of the right hepatic artery was employed in five of six patients to avoid infusing the right gastric artery, leaving the left lobe untreated (7). In another report, the gastroduodenal artery was, if necessary, embolized to exclude extrahepatic perfusion, but this technique ignores small extrahepatic branches of the proper hepatic artery which may not be seen angiographically, but which may result in extrahepatic deposition of

microspheres. By examining the hemodynamics of the hepatic arterial flow, and manipulating them with the balloon catheter, we were able to treat the entire liver in all patients without detectable extrahepatic perfusion.

Prior to the therapeutic administration of the ^{90}Y glass microspheres $^{99\text{m}}\text{Tc}$ -MAA was used to monitor the regional perfusion of the arterial catheter and to calculate the lung shunt. Like others (6,7), we assumed that $^{99\text{m}}\text{Tc}$ -MAA accurately predicted the behavior of the ^{90}Y microspheres. However, the glass microspheres are rigid and dense (3.29 g/cc), as compared to the lighter malleable MAA particles. Ideally a glass microsphere with the same physical characteristics as the ^{90}Y spheres, but labeled with a gamma-emitting isotope more suitable for imaging, would be employed, but were not available at the time of this trial. The use of a true tracer microsphere would also allow more accurate dosimetry estimations to be made (25).

The use of ^{86}Y -labeled analogs of ^{90}Y therapeutic radiopharmaceuticals has been suggested as the positron emission of ^{86}Y would not only permit PET imaging but has the potential for absolute quantification, an important consideration in dosimetry (26). The relative tumor to liver disposition of microspheres could be determined, and if the absolute liver and tumor volumes were known, the absorbed dose to normal liver and tumor could be calculated. Nevertheless, despite the potential differences in distribution between $^{99\text{m}}\text{Tc}$ -MAA and ^{90}Y glass microspheres, scintigraphy revealed at least qualitative similarity in biodistribution (Fig. 2). Thus larger areas of increased $^{99\text{m}}\text{Tc}$ -MAA deposition could be shown to receive increased quantities of ^{90}Y microspheres. The smaller areas of $^{99\text{m}}\text{Tc}$ -MAA deposition could not, however, be examined due to the lower resolution of the bremsstrahlung scans. A similar approach to monitoring the *in vivo* biodistribution of ^{90}Y glass microspheres has been employed by others (27).

While the perfusion ratio between tumor and normal liver could be estimated for $^{99\text{m}}\text{Tc}$ -MAA from profiles through tumors depicted by SPECT, this was not possible for the ^{90}Y bremsstrahlung studies. Nevertheless, the tumor-to-normal liver ratio of 2.86 ± 1.75 (range 1–17 to 8–83) is very similar to the mean ratio 3:1 (maximum 14:1) obtained by Yan et al. (27) with hepatomas. The latter were degraded by the broad energy spectrum of ^{90}Y bremsstrahlung and the downscatter and septal penetration by its high-energy components. The problems of imaging the bremsstrahlung from high-energy beta emitters are well recognized (28). In our patients, the problem was made more difficult by the need to set the energy window above that of $^{99\text{m}}\text{Tc}$ due to the previously administered $^{99\text{m}}\text{Tc}$ -MAA. The high energy, low abundance tail of the continuous bremsstrahlung spectrum can significantly degrade the quality of images by downscatter and septal penetration even when “high energy” ^{131}I collimators are used. Indeed collimators optimized for energies of 500–600 keV have been recommended (28).

Based on our preclinical investigation, we believed that a pulmonary dose of 10 mCi (resulting in about 1800 cGy to

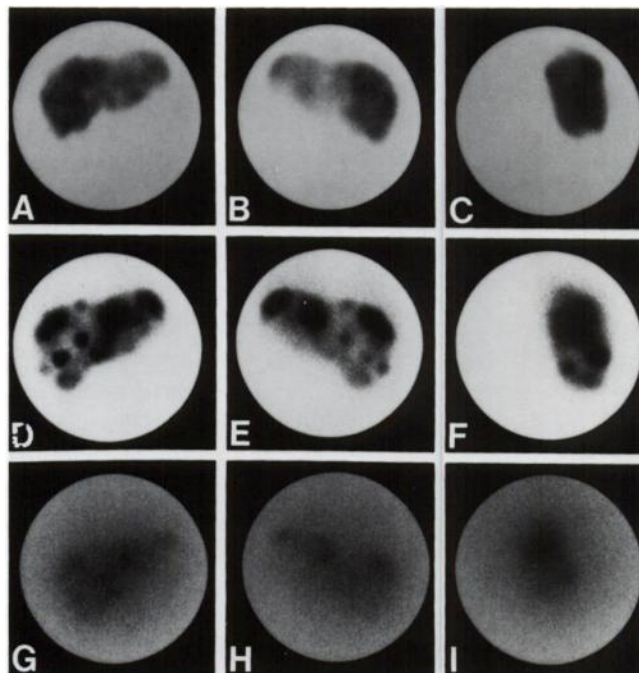


FIGURE 2. Studies in a patient with metastatic gastrinoma. (A–C) Technetium-99m-sulfur colloid liver scans (anterior, posterior and right lateral projections). Note multiple photopenic areas corresponding to multiple metastases. (D–F) Technetium-99m-MAA perfusion scans (anterior, posterior and right lateral projections). Note multiple areas of increased tracer deposition relative to photopenic liver (mean ratio 4.44) many of which correspond to photopenic areas on the sulfur colloid scan. (G–I) Post-therapy ^{90}Y Bremsstrahlung scans (anterior, posterior and right lateral projections). Note that although the quality of the image is degraded by blurring there is increased ^{90}Y deposition in areas of the liver which correspond to some of the foci of most prominent $^{99\text{m}}\text{Tc}$ -MAA deposition.

the lungs) or less, was unlikely to result in significant pulmonary toxicity, which was confirmed by these current clinical data. In the preclinical study, performed in mixed breed hounds, an intravenous dose of microspheres to achieve a whole-lung dose of 3000 cGy failed to result in any clinical, radiographic or histologic changes in the lungs, while doses of microspheres delivering 12,000–16,800 cGy led to severe pulmonary fibrosis (unpublished data).

An alternative radiopharmaceutical used for the hepatic arterial treatment of hepatomas has been ^{131}I -lipiodol (29). Dosimetric calculations in this setting show a similar differential delivery of radiation (liver metastases $6,240 \pm 5,400$ cGy, range 1,000–26,000; normal liver 550 ± 870 cGy, range 20–1,070; lung irradiation 290 ± 220 cGy, range 20–1,070).

Although the primary goal of this study was not to examine the efficacy of treatment with ^{90}Y microspheres, the response data (partial responses in 5 of 24 patients, a mean survival in the patients with colorectal cancer of 60 wk and 3 long-term survivors beyond 200 wk) for this group of heavily pretreated patients indicates potential activity warranting further evaluation of the modality (Fig. 3). It is important to note that the median survival for untreated

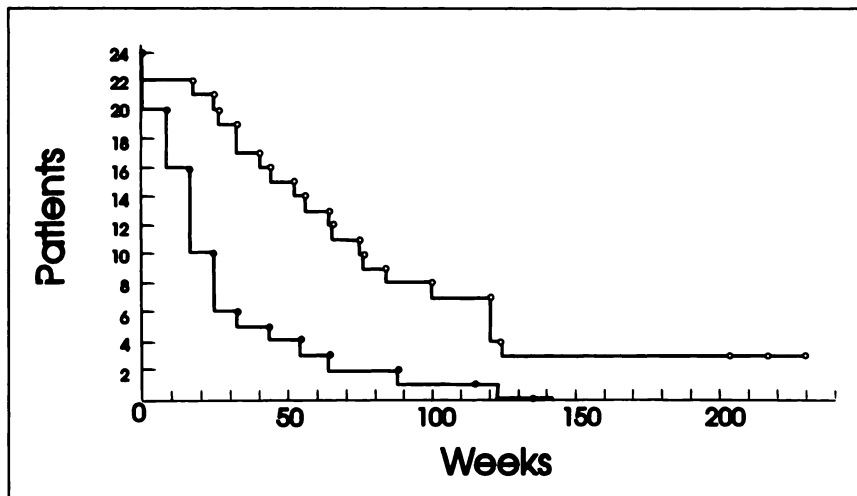


FIGURE 3. Kaplan-Meier curves showing times from treatment to tumor progression (closed circles) and to death (open circles). Data available for all 24 patients.

hepatic metastases from colorectal cancer is 2–10 mo, that of hepatoma 1–6 mo and that of metastatic carcinoids and neuroendocrine tumors only slightly better (30–34).

Similar encouraging preliminary data from ^{90}Y glass microsphere radioembolization have been obtained by other investigators. Herba et al. (6) describe symptomatic responses, CT changes suggestive of tumor response and relief of inferior vena cava obstruction; Goldberg et al. (35) describe all seven patients treated as “enjoying a period of control of their liver secondaries;” and Yan et al. (27) report 13 of 18 patients with hepatoma having greater than 50% reductions in tumor mass and alpha fetoprotein.

Future investigations with this agent will include escalation of the dose to determine the maximum tolerated dose, evaluation of therapeutic efficacy at or near maximum tolerated dose, the addition of pretreatment with radiosensitizing drugs such as bromodeoxyuridine (36,37) and tumor blood flow modulation with vasoactive drugs to further improve the ratio of tumor-to-liver radiation delivery (35,38,39) and better quantify the radiation dose distribution from the microspheres (21,22,26,28).

ACKNOWLEDGMENTS

The authors wish to thank the nursing staff of the Clinical Research Center for the care of patients and Ms. Joan Fogarty for manuscript preparation. Supported in part by NIH grants CA-33825 and MO1-RR00042. The radiopharmaceutical (^{90}Y glass microspheres) was donated by Therogenics, Atlanta, GA.

REFERENCES

1. Gyves JW, Zeissman HA, Ensminger WD, et al. Definition of hepatic tumor microcirculation by single photon emission computerized tomography (SPECT). *J Nucl Med* 1984;25:972–977.
2. Grady ED. Internal radiation therapy of hepatic cancer. *Dis Col Rect* 1979;22:371–375.
3. Ariel IM, Pack GT. Treatment of inoperable cancer of the liver by intraarterial radioactive isotopes and chemotherapy. *Cancer* 1967;20:793–803.
4. Mantravadi RVP, Spigos DG, Tan WS, Felix EL. Intraarterial yttrium-90 in the treatment of hepatic malignancy. *Radiology* 1982;142:783–786.
5. Ehrhardt GJ, Day DE. Therapeutic use of ^{90}Y microspheres. *Nucl Med Biol* 1987;14:233–242.
6. Herba MF, Illescas FF, Thirlwell MP, et al. Hepatic malignancies: improved treatment with intraarterial ^{90}Y . *Radiology* 1988;169:311–314.

7. Houle S, Yip TCK, Shepherd FA, et al. Hepatocellular carcinoma: pilot trial of treatment with ^{90}Y microspheres. *Radiology* 1989;172:857–860.
8. Chuang VP, Wallace S. Hepatic arterial redistribution for intraarterial infusion of hepatic neoplasms. *Radiology* 1980;135:295–299.
9. Nakamura H, Tanaka M, Hiromichi O. Hepatic embolization from the common hepatic artery using balloon occlusion technique. *AJR* 1985;145:115–116.
10. Andrews JC, Williams DM, Shapiro B, Ensminger WD. Low infusion rate digital subtraction angiography to predict regional perfusion in hepatic arterial chemotherapy. *Cardiovasc Intervent Radiol* 1989;12:277–280.
11. Ziessman HA, Thrall JH, Yang PJ, et al. Hepatic arterial perfusion scintigraphy with ^{99m}Tc -MAA. *Radiology* 1984;152:167–172.
12. Zeissman HA, Wahl RL, Juni JE, et al. The utility of SPECT for ^{99m}Tc -MAA hepatic arterial perfusion scintigraphy. *AJR* 1985;145:747–751.
13. Wahl RL, Zeissman HA, Juni J, Lahti D. Gastric air contrast: useful adjunct to hepatic artery scintigraphy. *AJR* 1984;143:321–325.
14. Ziessman HA, Gyres JW, June JE, et al. Atlas of hepatic arterial perfusion scintigraphy. *Clin Nucl Med* 1985;10:676–681.
15. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457–481.
16. Gray BN, Burton MA, Kelleher D, Klemp P, Matz L. Tolerance of the liver to the effects of yttrium-90 radiation. *Int J Rad Onc Biol Phys* 1990;18:616–623.
17. Wollner I, Knutsen C, Smith P, et al. Effects of hepatic arterial yttrium-90 glass microspheres in dogs. *Cancer* 1988;61:1336–1344.
18. Ingold JA, Reed GB, Kaplan HS, Bagshaw MA. Radiation hepatitis. *AJR* 1965;93:200–208.
19. Wharton JT, Declos L, Gallager W, Smith JP. Radiation hepatitis induced by abdominal irradiation with cobalt-60 moving strip technique. *AJR* 1973;117:73–80.
20. Kassis AJ. The MIRD approach: remembering the limitations. *J Nucl Med* 1992;33:781–782.
21. Shapiro B, Fig LM. General principles and perspectives of cancer therapy with radiopharmaceuticals. *J Nucl Med Allied Sci* 1990;34:260–264.
22. Roberson PL, Ten Haken RK, McShan DL, McKeever PE, Ensminger WD. Three-dimensional tumor dosimetry for hepatic yttrium-90 microsphere therapy. *J Nucl Med* 1992;33:735–738.
23. Cripps C, Thirlwell M, Boos G, Blanchard R, Belzberg A. Phase I-II study of hepatic arterial yttrium-90 glass microsphere (Therasphere) therapy for liver neoplasia [Abstract]. *ASCO Proc* 1990;9:115.
24. Marn CS, Andrews JC, Francis IR, Hollet MD, Walker SC, Ensminger WE. Hepatic parenchymal changes after intra-arterial ^{90}Y therapy: CT findings. *Radiology* 1993;187:125–128.
25. Curtis RL, Lattimer JC, Ehrhardt GJ, et al. Pre-operative radiotherapy of renal cell carcinoma using intra-arterial ^{153}Sm activatable glass microspheres [Abstract]. *J Nucl Med* 1991;32:1089.
26. Herzog H, Rösch F, Stocklin G, Lueders C, Qaim SM, Feinendegen LE. Measurement of pharmacokinetics of yttrium-86 radiopharmaceuticals with PET and radiation dose calculation of analogous yttrium-90 radiotherapeutics. *J Nucl Med* 1993;34:2222–2226.
27. Yan Z-P, Lin G, Zhao H-Y, Dong Y-H. An experimental study and clinical

- pilot trials on yttrium-90 glass microspheres through the hepatic artery for treatment of primary liver cancer. *Cancer* 1993;72:3210-3215.
28. Clarke LP, Cullom SJ, Shaw R, et al. Bremsstrahlung imaging using the gamma camera: factors affecting attenuation. *J Nucl Med* 1992;33:161-166.
 29. Raoul JI, Bretagne JF, Caucanas JP, et al. Internal radiation therapy for hepatocellular carcinoma: results of a french multicenter phase II trial of transarterial injection of iodine-131-labeled lipiodol. *Cancer* 1992;69:346-352.
 30. Oberfield RA, Steele G, Gollan JL, Sherman D. Liver cancer. *CA* 1989;39:206-218.
 31. Cady B. Natural history of primary and secondary tumors of the liver. *Semin Oncol* 1983;10:127-134.
 32. Nelson RS, Elizalde R, Howe CD. Clinical aspects of primary carcinoma of the liver. *Cancer* 1966;19:533-537.
 33. Jaffe BM, Donegan WL, Watson F, et al. Factors influencing untreated hepatic metastases. *Surg Gynecol Obstet* 1968;127:1-8.
 34. Primack A, Vogel CL, Kyalwazi SK, et al. A staging system for hepatocellular carcinoma: prognostic factors in Uganda patients. *Cancer* 1975;35:1356-1368.
 35. Goldberg JA, Anderson JH, Bessent RG, et al. Glass ⁹⁰Y microspheres and angiotensin II for colorectal liver metastases [Abstract]. *Nucl Med Commun* 1991;12:256.
 36. Kinsella TJ, Mitchell JB, Russo A, et al. Continuous intravenous infusions of bromodeoxyuridine as a clinical radiosensitizer. *J Clin Oncol* 1984;2:1144-1150.
 37. Ensminger WD, Andrews JC, Walker-Andrews S, et al. Pharmacokinetics of 5-bromo-2'-deoxyuridine (Brd Urd) applicable to hepatic arterial infusion [Abstract]. *ASCO Proc* 1989;8:77.
 38. Andrews JC, Walker-Andrews SC, Juni JE, Warber S, Ensminger WD. Modulation of liver tumor blood flow with hepatic arterial epinephrine: a SPECT study. *Radiology* 1989;173:645-647.
 39. Burton MA, Gray BN, Self GW, Heggie JC, Townsend PS. Manipulation of experimental rat and rabbit tumor blood flow with angiotensin II. *Cancer Res* 1985;45:5390-5393.

EDITORIAL

Microdosimetric Considerations of Hepatic Radioembolization

Tumor therapy is constrained by the demand to limit damage to normal tissue while arresting or at least slowing the growth and spread of the tumor. Chemotherapy and radiotherapy from external sources are restricted by the harm they may impose on essential body function through detriment to normal cells either near or distant from the tumor. Localizing the therapeutic intervention (be it from a chemical or physical agent) primarily to tumor cells without affecting normal cells may be approached by at least two avenues: first, by using specific cell-recognition systems for toxic agents, either through receptors or metabolic states of tumor cells that are not shared by normal cells at the tumor site when the agent is applied (1) and, second, by transporting the bulk of the toxic agent to the tumor, either by implanting sources within, or delivering particle sources via the blood circulation to the tumor. Both of these avenues are within the domain of nuclear medicine; two outstanding examples are the therapeutic application of monoclonal antibodies carrying a suitable radionuclide for lethal irradiation of receptor-specific tumor cells and brachytherapy, and brachyradiotherapy on the microscopic level. Radioembolization of tumor as described

by Andrews et al. in this issue of the *Journal* (2) is a fascinating example of the latter.

Full clinical acceptance of the approach pioneered in a number of centers, especially by Andrews et al. (2), requires attention to the behavior and stability of microparticles in the blood circulation, the radionuclide that is bound to them, the mode of delivery of the particles to the tumor with regard to the eventual concomitant exposure of normal tissue, and finally, to the optimization of embolization of the tumor vasculature. All efforts have the common denominator of a most favorable ratio of absorbed doses to tumor cells and normal tissue. In view of the technical difficulties and the need to address them, Andrews et al.'s paper is an exemplary, careful and innovative approach to these challenging problems.

By selecting glass microspheres with a diameter of 22 μ m, which were introduced in 1987 (3), difficulties that arose from the premature release of the radionuclide due to the disintegration in vivo of organic polymer microspheres were overcome (4). Andrews et al. (2) solved the problem of optimal delivery of the microspheres to the site of attempted irradiation in the case of liver tumors by assessing blood flow by angiography and sulfur-colloid scintigraphy, and by blocking extrahepatic circulation from aberrant hepatic arteries by angiographic ma-

nipulations. Further increases in the ratio of microsphere deposition in tumor versus normal liver tissue could favor widespread clinical acceptance of the ⁹⁰Y-microsphere brachytherapy technique. Two principal kinds of modalities might be considered to enhance tumor perfusion: pharmacological and physical. The first, as mentioned by Andrews et al. (2), is exemplified by vasoactive drugs such as angiotensin II (5) and epinephrine (6). The second could use pre-irradiation of the tumor with 6-9 Gy from a gamma source (7). Localized hyperthermia may be another valuable adjuvant to radioembolization of liver tumors. A radiation sensitizer like bromodeoxyuridine has also been considered (4).

Having minimized the transport and trapping of microspheres outside the liver by obstructing passage into the extrahepatic circulation (e.g., into the lung) and optimizing the infusion rate, the values of absorbed doses that are eventually delivered to tumor and normal liver tissue from the ⁹⁰Y that was engineered to be tightly bound within the glass microspheres are of crucial importance. The heterogeneous microdistribution of particles in the circulation of the target tissue is a formidable obstacle to modeling the anticipated relation of the biological effect of radiation on the average physical absorbed dose to the tumor.

The conventional mode of express-

Received May 10, 1994; accepted June 1, 1994.
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