Treatment of Unresectable Hepatocellular Carcinoma with Intrahepatic Yttrium 90 Microspheres: Factors Associated with Liver Toxicities

James E. Goin, PhD, Riad Salem, MD, MBA, Brian I. Carr, MD, PhD, Janet E. Dancey, MD, Michael C. Soulen, MD, Jean Francois H. Geschwind, MD, Kathleen Goin, MS, Mark Van Buskirk, MS, and Kenneth Thurston, MA

PURPOSE: Intraarterial injection of yttrium 90 microspheres (TheraSpheres) is used in the treatment of hepatocellular carcinoma (HCC). This article presents an analysis of the incidence of liver toxicities (liver-related events) and pretreatment factors associated with liver toxicities after TheraSphere treatment.

PATIENTS AND METHODS: Eighty-eight TheraSphere-treated patients with low 90-day mortality risk were selected for analysis, with liver toxicities coded with use of standard oncology criteria. Descriptive and inferential statistical methods were applied to estimate the incidence of liver toxicities and to evaluate the influence of liver radiation dose and various pretreatment factors on the risk of their occurrence.

RESULTS: Sixty-eight liver toxicities occurred in 37 of the 88 patients (42%). Thirty-two patients (36%) experienced 50 liver toxicities after the first treatment and nine of 23 patients (39%) who received a second treatment experienced 18 liver toxicities. Pretreatment total bilirubin and liver radiation dose were found to be associated with the risk of at least one liver toxicity and with the time to first occurrence of a liver toxicity after first treatment. Pretreatment total bilirubin also was associated with liver toxicities after the second treatment. Most of the toxicities resolved; however, those that did not resolve were attributed to tumor progression or advancing cirrhosis.

CONCLUSIONS: The risk of liver toxicities in patients with unresectable HCC treated with TheraSpheres increases with increasing pretreatment total bilirubin level and liver radiation dose to a maximum of 150 Gy for a single administration. The toxicities attributed to treatment resolved over time, and none of the patients studied had confirmed radiation-induced liver disease. Consequently, doses as high as 150 Gy on a single administration and as high as 268 Gy on repeated administrations were well tolerated.

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Abbreviations: CLIP = Cancer of the Liver Italian Program, HCC = hepatocellular carcinoma, RILD = radiation-induced liver disease

From DataMedix Corporation (J.E.G., K.G., M.V.B., K.T.), Brookhaven; Thomas E. Starzl Transplantation Institute (B.I.C.), Pittsburgh; Division of Interventional Radiology (M.C.S.), Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania; Department of Radiology (R.S.), Northwestern Memorial Hospital, Chicago, Illinois; Investigational Drug Branch (J.E.D.), Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Rockville; and Division of Cardiovascular and Interventional Radiology (J.F.H.G.), The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, Maryland. Received May 3, 2004; revision requested June 16; final revision received and accepted August 2. **Address correspondence to** R.S., Northwestern Memorial Hospital, Department of Radiology, 676 N. St. Claire, Suite 800, Chicago, IL 60611; E-mail: r-salem@northwestern.edu

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TRADITIONAL whole-liver external-beam radiation therapy has had limited use in the treatment of unresectable hepatocellular carcinoma (HCC) because the liver parenchyma is relatively radiation-sensitive and is unable to tolerate the radiation dose required to achieve tumoricidal effects. Even in patients with noncompromised liver function, when exposed to uniform radiation fields with use of conventional fractionation, the liver can tolerate only 30–35 Gy (1–3). It has been estimated that a 50% incidence of radia-

Table 1
Distribution of Number of Patients/Treatments and Liver Dose By Center

Center	Number of Patients/Treatments	Liver Dose (Gy)					
		Per Treatment			Accumulated*		
		Median	Minimum	Maximum	Median	Minimum	Maximum
DR†	8/8	85	34	105	85	34	105
TGH†	17/19	102	27	145	107	47	209
UPMC‡	51/70	130	51	153	135	61	266
HUP‡	7/9	125	69	146	136	90	243
JHU‡	5/7	138	129	148	139	137	268
All patients	88/113	128	27	153	130	34	268

* Volume-weighted average.
† Before Humanitarian Device Exemption.
‡ After Humanitarian Device Exemption.
Note.—DR = dose ranging (Toronto General Hospital, $n = 5$; University of Michigan Hospital, $n = 1$; The Montreal General Hospital, $n = 1$; Ottawa Regional Cancer Centre, $n = 1$); TGH = Toronto General Hospital; UPMC = University of Pittsburgh Medical Center; HUP = Hospital of the University of Pennsylvania; JHU = The Johns Hopkins University Hospital. Dates of first treatment: DR, 07/24/86; TGH, 04/03/92; UPMC, 08/15/00; HUP, 08/21/01; JHU, 07/16/01.

tion-induced liver disease (RILD) could be expected with a whole-liver dose of 35 Gy (4). However, recent data suggest that the liver is somewhat more radiation-tolerant, with a 50% incidence of RILD at a mean liver dose of 40 Gy, when radiation is used in combination with fluorodeoxyuridine in patients with primary hepatobiliary cancer (5). The relative radiation intolerance of liver parenchyma combined with the radiation resistance of HCC has led to the use of conformal radiation therapy for treatment of HCC, allowing deposition of higher doses of radiation in smaller volumes of liver to boost tumoricidal effect and spare liver parenchyma (5–7).

TheraSphere (MDS Nordion, Ottawa, ON, Canada), a treatment for unresectable HCC, consists of yttrium 90 embedded into nonbiodegradable glass microspheres, which can be administered by intraarterial hepatic injection. HCC tumors are generally highly vascular and receive the majority of their blood supply from the hepatic artery, compared with liver parenchyma, which receives its blood supply primarily from the portal vein. Therefore, the intraarterial injection of ^{90}Y microspheres represents treatment that can be delivered in a local (segmental or subsegmental), regional (lobar via left or right hepatic artery), or whole-liver (via proper hepatic artery) manner, resulting in high radiation doses to tumor while sparing liver parenchyma. This method of treatment takes full advantage of the safety margin provided by distributing the radiation in a partial liver volume while allowing tumors to receive tumoricidal doses of radiation. In addition, external-beam radiation therapy provides a uniform but varying field over tissue volumes, whereas ^{90}Y microspheres provide millions of scattered point sources of radioactivity. Therefore, for a given measure of absorbed dose, the two methods have different biologic effects (8).

The purpose of this article is to present the findings of a retrospective analysis of liver toxicities, and the factors influencing those toxicities, after TheraSphere treatment in 88 selected patients who received mean partial liver volume doses ranging from 27 Gy to 268 Gy. The 88 patients were selected from a larger database containing data on a heterogeneous group of 121 TheraSphere-treated patients, and comprise a group of patients with low 90-day mortality risk (9).

PATIENTS AND METHODS

Patients Treated

The distribution of the number of patients and treatments by study center is provided in **Table 1**. The study protocols were approved by each participating center's institutional review board or ethics committee, and all patients signed an informed consent allowing use of their data. Data used in the analysis represent patients classified as having a low 90-day mortality risk (9). Briefly, the selection criteria identified patients with unresectable HCC who did not have HCC of infiltrative type, bulk disease (≥70% tumor replacement of liver), tumor replacement of liver of at least 50% with an albumin level less than 3.0 g/dL, previous intraarterial liver-directed treatment, aspartate or alanine aminotransferase levels greater than five times the upper limit of normal, total bilirubin level at least 2 mg/dL, previous external-beam liver radiation therapy, or evidence of any uncorrectable flow to the gastrointestinal tract and greater than 30 Gy estimated accumulated dose delivered to the lungs as observed on angiography or technetium 99 macroaggregated albumin scan.

TheraSphere Treatment

The treatment approach was to treat the liver lobe affected if the patient presented with unilobar disease (ie, regional treatment). The treatment approach for patients presenting with bilobar disease differed between early and later study protocols. In the first two studies (**Table 1**), patients presenting with bilobar disease received whole-liver treatment (catheter inserted into the proper hepatic artery). In the later studies (**Table 1**), the lobe with the dominant tumor burden was treated first, and if the tumor in the