^{90}Y Radioembolization of Colorectal Hepatic Metastases Using Glass Microspheres: Safety and Survival Outcomes from a 531-Patient Multicenter Study

Ryan Hickey[1], Robert J. Lewandowski[1], Totianna Prudhomme[2], Eduardo Ehrenwald[2], Brian Baigorri[3], Jeffrey Critchfield[3], Joseph Kallini[1], Ahmed Gabr[1], Boris Gorodetski[4], Jean-Francois Geschwind[4], Andrea Abbott[5], Ravi Shridhar[6], Sarah B. White[7], William S. Rilling[7], Brendan Boyer[8], Shannon Kauffman[8], Sharon Kwan[9], Siddarth A. Padia[9], Vanessa L. Gates[1], Mary Mulcahy[10], Sheetal Kircher[10], Halla Nimeiri[10], Al B. Benson[10], and Riad Salem[1,10]

[1]Section of Interventional Radiology, Department of Radiology, Robert H. Lurie Comprehensive Cancer Center, Northwestern Memorial Hospital, Chicago, Illinois; [2]Department of Interventional Radiology, Abbott Northwestern Hospital, Minneapolis, Minnesota; [3]Department of Radiology, Detroit Medical Center, Wayne State University, Detroit, Michigan; [4]Interventional Radiology Center, Johns Hopkins Hospital, Baltimore, Maryland; [5]Department of Surgery, Moffitt Cancer Center, Tampa, Florida; [6]Department of Radiation Oncology, Moffitt Cancer Center, Tampa, Florida; [7]Division of Vascular/Interventional Radiology, Department of Radiology, Medical College of Wisconsin, Milwaukee, Wisconsin; [8]Department of Radiology, Miami Valley Hospital, Dayton, Ohio; [9]Section of Interventional Radiology, Department of Radiology, University of Washington, Seattle, Washington; and [10]Division of Hematology and Oncology, Department of Medicine, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, Illinois

Hepatic metastases of colorectal carcinoma are a leading cause of cancer-related mortality. Most colorectal liver metastases become refractory to chemotherapy and biologic agents, at which point the median overall survival declines to 4–5 mo. Radioembolization with ^{90}Y has been used in the salvage setting with favorable outcomes. This study reports the survival and safety outcomes of 531 patients treated with glass-based ^{90}Y microspheres at 8 institutions, making it the largest ^{90}Y study for patients with colorectal liver metastases. **Methods:** Data were retrospectively compiled from 8 institutions for all ^{90}Y glass microsphere treatments for colorectal liver metastases. Exposure to chemotherapeutic or biologic agents, prior liver therapies, biochemical parameters before and after treatment, radiation dosimetry, and complications were recorded. Uni- and multivariate analyses for predictors of survival were performed. Survival outcomes and clinical or biochemical adverse events were recorded. **Results:** In total, 531 patients received ^{90}Y radioembolization for colorectal liver metastases. The most common clinical adverse events were fatigue (55%), abdominal pain (34%), and nausea (19%). Grade 3 or 4 hyperbilirubinemia occurred in 13% of patients at any time. The median overall survival from the first ^{90}Y treatment was 10.6 mo (95% confidence interval, 8.8–12.4). Performance status, no more than 25% tumor burden, no extrahepatic metastases, albumin greater than 3 g/dL, and receipt of no more than 2 chemotherapeutic agents independently predicted better survival outcomes. **Conclusion:** This multiinstitutional review of a large cohort of patients with colorectal liver metastases treated with ^{90}Y radioembolization using glass microspheres has demonstrated promising survival outcomes with low toxicity and low side effects. The outcomes were reproducible and consistent with prior reports of radioembolization.

Received Aug. 26, 2015; revision accepted Nov. 30, 2015.

For correspondence or reprints contact: Riad Salem, Department of Radiology, Northwestern Memorial Hospital, 676 N. St. Clair, Suite 800, Chicago, IL 60611.

E-mail: r-salem@northwestern.edu

Published online Dec. 3, 2015.

Key Words: radioembolization; colorectal metastases; survival; ^{90}Y

J Nucl Med 2016; 57:665–671

DOI: 10.2967/jnumed.115.166082

Metastases of colorectal carcinoma are the third most common cause of cancer-related mortality worldwide. Advances in chemotherapy regimens, biologic agents, and liver resection in select cases have prolonged overall survival after the diagnosis of hepatic metastases. Nonetheless, most colorectal liver metastases become refractory or resistant to these regimens, at which point survival estimates range from 4 to 5 mo. ^{90}Y radioembolization of hepatic metastases has been increasingly used in this salvage setting and has shown favorable survival outcomes—exceeding 10 mo—after ^{90}Y radioembolization (*1–3*). Most of the published outcomes have been after ^{90}Y radioembolization using resin microspheres. However, a substantial number of patients with colorectal liver metastases undergo ^{90}Y radioembolization with glass microspheres. This paper reports the survival and safety outcomes of 531 patients with hepatic metastases of colorectal cancer treated with glass ^{90}Y microspheres at several institutions.

MATERIALS AND METHODS

Patient Cohort

Between 2001 and 2014, 531 consecutive patients underwent radioembolization of hepatic metastases of colorectal carcinoma at 8 institutions. The study was approved by Institutional Review Boards and was compliant with the Health Insurance Portability and Accountability Act. Data were retrospectively compiled into a common database and analyzed at a single institution. The clinical trials registration number was NCT00532740.

This report complies with the research reporting standards for radioembolization (*4*). Clinical side effects and biochemical toxicity according

to version 4.0 of National Cancer Institute common terminology criteria were recorded at follow-up. Clinical adverse events and biochemical toxicity occurring at any time after treatment were recorded (not limited to 30 d).

The study represents retrospectively collected data at cancer centers with expertise in locoregional therapies. The indications for ^{90}Y radioembolization included unresectable metastases from colorectal cancer; imaging-confirmed progressive disease refractory to previous systemic or locoregional therapy; an Eastern Cooperative Oncology Group (ECOG) status of no more than 2; the ability to undergo angiography and selective visceral catheterization; and adequate hematology counts (granulocytes $\geq 1.5 \times 10^9$/L and platelets $\geq 50 \times 10^9$/L), renal function (creatinine $\leq$ 2.0 mg/dL), and liver function (bilirubin $\leq$ 2.0 mg/dL). Exclusion criteria included significant extrahepatic disease (life expectancy $<$ 3 mo); angiographic evidence or ^{99m}Tc-macroaggregated albumin scan evidence of uncorrectable gastrointestinal flow; or an estimated lung dose of more than 30 Gy in a single session.

Patient Evaluation and Workup

All patients underwent baseline laboratory tests and radiologic imaging within 1 mo of treatment. Imaging information was used to determine baseline tumor burden, uni- or multifocality, and presence or absence of extrahepatic metastases. Pretreatment angiography was performed to determine proper catheter positioning and to identify any collateral flow to the gastrointestinal tract (*5–9*). ^{99m}Tc-macroaggregated albumin scanning was performed to detect gastrointestinal flow and lung shunt fraction (*6*). Prophylactic embolization of aberrant vessels was performed when appropriate.

Treatment Plan

All radioembolization procedures were performed with a glass-based ^{90}Y device (TheraSphere; BTG International Ltd.). This device is currently approved for hepatocellular carcinoma in the United States and for liver neoplasia worldwide (*10*). The method for determining the injected activity required to deliver 120 Gy has been published previously (*4,6,11,12*).

Overall Survival

Median overall survival was calculated from the dates of diagnosis of the primary cancer, hepatic metastases, and first ^{90}Y treatment, censored to the date of last follow-up. Survival analyses were substratified on the basis of exposure to cytotoxic chemotherapeutics (5-fluorouracil/capecitabine, oxaliplatin, or irinotecan) and biologic agents (bevacizumab, cetuximab/panitumumab, or regorafenib).

Uni- and Multivariate Analyses and Statistical Plan

Uni- and multivariate analyses were performed using the Cox proportional hazards model. The variables entered into the univariate analyses included patient demographics (sex and age), performance status (ECOG), prior therapy (cytotoxic or biologic agents), presence of metastatic disease at diagnosis, tumor burden, presence of extrahepatic metastases, and liver function. Variables with a P value of no more than 0.25 by the univariate model were included in the multivariate model. Analyses were performed using SPSS Statistics (version 22.0; IBM), with a P value of less than 0.05 considered significant.

RESULTS

Baseline Characteristics

Most patients (63%) were less than 65 y old at the time of treatment (59% were male), most (96%) had an ECOG status of 0 or 1, most (70%) had tumor in no more than 25% of the liver volume, and most (62%) had liver-only disease (38% had limited extrahepatic disease). Eighteen percent of patients had prior hepatic resection, 14% had prior liver ablation, and 4% had prior transarterial chemoembolization (Table 1).

TABLE 1
Baseline Characteristics

Characteristic	*n*
Age (y)	
65	334 (63%)
≥65	197 (37%)
Sex	
Male	314 (59%)
Female	217 (41%)
Tumor burden	
≤25%	370 (70%)
26%–50%	103 (19%)
50%	58 (11%)
Stage IV* at diagnosis	242 (46%)
Extrahepatic disease	
Absent	329 (62%)
Present	202 (38%)
ECOG 0 or 1	509 (96%)
Albumin ≤ 3 g/dL	106 (20%)
Bilirubin > 1.3 mg/dL	39 (7%)
Prior liver therapy	
None	275 (71%)
Chemoembolization	22 (4%)
Ablation	73 (14%)
Resection	98 (18%)

*American Joint Committee on Cancer criteria.

Before ^{90}Y radioembolization, 56% of patients received 3 cytotoxic chemotherapeutics (5-fluorouracil, oxaliplatin, and irinotecan), whereas 41% received only 1 or 2 of these agents and 3% received none of these agents. Twenty-two percent of patients received no biologic agents, 56% received 1 biologic agent, and 22% received 3 biologic agents (Table 2).

Nearly all patients underwent lobar or selective radioembolization at the first treatment. Only 2% of patients received whole-liver treatment in a single setting.

^{90}Y Dosimetry and Delivery

The median radiation dose delivered to the liver was 120.2 Gy (range, 35–391 Gy). In all cases, 90% or more of the dose was delivered. Extrahepatic arterial coil embolization was performed in 25% of patients.

Side Effects and Biochemical Toxicity

The most frequent clinical side effects included fatigue (55%), abdominal pain or discomfort (34%), and nausea (19%). Vomiting, anorexia, and fever occurred in less than 10% of patients (Table 3). No gastrointestinal ulcers were reported.

Grade 3 or 4 biochemical toxicity, recorded at any time after treatment, included effects on the levels of bilirubin (13%), alkaline phosphatase (9%), albumin (8%), aspartate transaminase (3%), and alanine transaminase (<1%) (Table 4).

TABLE 2
Cytotoxic Chemotherapies and Biologic Agents

Agent	*n*
Cytotoxic chemotherapy (5-fluorouracil, oxaliplatin, irinotecan)	
None	15 (3%)
1–2	216 (41%)
3	295 (56%)
Biologic therapy (bevacizumab, cetuximab, panitumumab, regorafenib)	
None	114 (21%)
1	295 (56%)
2	117 (22%)
3	4 (<1%)
4	1 (<1%)

Overall Survival

At the time of data compilation, 284 patients had died. Survival analysis is provided in Tables 5–8. Median overall survival was 48.7 mo (95% confidence interval [95% CI], 44.2–53.2) from the date of diagnosis of the primary tumor, censored to the last follow-up; 37.7 mo (95% CI, 33.7–41.7) from diagnosis of hepatic metastases; and 10.6 mo (95% CI, 8.8–12.4) from the first ^{90}Y treatment. The median time from diagnosis of hepatic metastases to the first ^{90}Y treatment was 17.5 mo (95% CI, 15.2–19.7). Median overall survival from the first ^{90}Y treatment was longer in patients without extrahepatic disease than in those with extrahepatic disease (14.4 vs. 6.6 mo, $P < 0.001$).

The time from diagnosis of hepatic metastases to the first ^{90}Y treatment was longer for patients who received 3 cytotoxic chemotherapeutics than for those who received 2 or fewer (22.6 vs. 10.9 mo, $P < 0.001$). Median overall survival from the first ^{90}Y treatment was shorter for patients who received 3 cytotoxic chemotherapeutics than for those who received 2 or fewer (9.2 vs. 14.7 mo, $P < 0.001$). Regarding patients without extrahepatic disease at the time of the first ^{90}Y treatment, median overall survival was longer for those receiving 2 or fewer cytotoxic chemotherapeutics than for those receiving 3 (16.5 vs. 13.1 mo, $P < 0.05$). Regarding patients with extrahepatic disease at the first ^{90}Y treatment, median overall survival was longer for those receiving 2 or fewer cytotoxic chemotherapeutics than for those receiving 3 (9.6 vs. 5.4 mo, $P = 0.003$).

Median overall survival after the first ^{90}Y treatment did not significantly differ between patients who received no biologic agents and those who received one (11.5 vs. 12.9 mo); was longer for patients who received 0 or 1 biologic agent than for those who received 2 or more (12.9 vs. 7.0 mo, $P < 0.001$); and was longer for patients treated after 2004 than for those treated before 2004 (10.9 vs. 7.0 mo, $P < 0.05$).

Uni- and Multivariate Analyses

Better survival outcomes were predicted by ECOG performance status 0 ($P < 0.001$), American Joint Committee on Cancer stage 3 or less at the time of diagnosis ($P = 0.113$), lack of extrahepatic metastases ($P < 0.001$), hepatic tumor burden of no more than 25% ($P < 0.001$), 2 or fewer cytotoxic chemotherapeutics ($P < 0.001$), no biologic therapy ($P < 0.001$), bilirubin less than 1.3 mg/dL ($P < 0.001$), and albumin greater than 3 g/dL ($P < 0.001$).

On multivariate analysis, ECOG performance status 0 (hazard ratio, 0.61; 95% CI, 0.46–0.79), hepatic tumor burden of no more than 25% (hazard ratio, 0.37; 95% CI, 0.28–0.49), no extrahepatic metastatic disease (hazard ratio, 0.50; 95% CI, 0.38–0.64), albumin greater than 3 g/dL (hazard ratio, 0.47; 95% CI, 0.35–0.63), and 2 or fewer cytotoxic chemotherapeutics (hazard ratio, 0.61; 95% CI, 0.46–0.79) independently predicted better survival outcomes (Table 9).

DISCUSSION

Colorectal carcinoma remains one of the most common cancers worldwide, with approximately half the affected individuals eventually developing liver metastases. Only a minority of these patients are candidates for potentially curative therapies such as surgical resection or ablation. Modern chemotherapy regimens and the advent of biologic agents have significantly prolonged the median overall survival of patients with hepatic metastases to approximately 29–32 mo (*13,14*). Nonetheless, once hepatic metastases become chemorefractory, survival estimates are poor, typically between 4 and 5 mo (*15–17*).

Transarterial ^{90}Y radioembolization has increasingly been used as a locoregional therapy for chemorefractory hepatic metastases and was recently included in the European Society for Medical Oncology clinical practice guidelines for the treatment of liver-limited colorectal metastases failing chemotherapeutic options (*18*). Radioembolization relies on the fact that the blood supply of hepatic tumors is different from that of normal liver parenchyma. Primary and metastatic hepatic tumors receive most of their blood supply from the hepatic arteries, as opposed to the predominantly portal venous blood supply of the liver parenchyma. Injection of

TABLE 3
Clinical Side Effects

Side effect	*n*
Fatigue	290 (55%)
Abdominal pain/discomfort	182 (34%)
Nausea	98 (19%)
Anorexia	36 (7%)
Fever/chills	36 (7%)
Vomiting	32 (6%)
Diarrhea	10 (2%)

TABLE 4
Grade 3–4 Biochemical Toxicity*

Toxicity affecting…	*n*
Bilirubin	69 (13%)
Alkaline phosphatase	46 (9%)
Albumin	40 (8%)
Aspartate transaminase	18 (3%)
Alanine transaminase	3 (<1%)

*National Cancer Institute common terminology criteria, version 4.0.

TABLE 5
Overall Survival

Interval (mo)	Median	*P*
From diagnosis of primary	48.7 (44.2–53.2)	
From diagnosis of hepatic metastases	37.7 (33.7–41.7)	
From first ^{90}Y treatment	10.6 (8.8–12.4)	
From hepatic metastases to ^{90}Y	17.5 (15.3–19.7)	
From ^{90}Y (no extrahepatic metastases) (n = 329)	14.4 (12.7–16.1)	<0.001
From ^{90}Y (with extrahepatic metastases) (n = 202)	6.6 (5.2–8.1)	

Ranges in parentheses are 95% CI.

radioactive microspheres into the hepatic artery leads to preferential deposition within tumor capillaries, providing antitumoral radiation effects that are not available in the standard treatment paradigms for colorectal liver metastases.

Several studies have shown ^{90}Y radioembolization to be beneficial in the treatment of metastatic colorectal cancer. A randomized phase II analysis of the addition of a single treatment of ^{90}Y resin microspheres to the standard regimen of 5-fluorouracil/leucovorin for patients with colorectal liver metastases found significantly prolonged median overall survival compared with the standard regimen alone (29.4 vs. 12.8 mo, P = 0.02) (*19*). The addition of ^{90}Y radioembolization to systemic chemotherapy has been shown to prolong the time to liver tumor progression in patients with chemorefractory colorectal liver metastases (5.5 vs. 2.1 mo, P = 0.003) (*20*), and matched-pair analysis of patients with chemorefractory colorectal liver metastases demonstrated a survival benefit for patients receiving ^{90}Y radioembolization compared with those receiving best supportive care (8.3 vs. 3.5 mo, $P < 0.001$) (*21*). A prospective multicenter phase II analysis of ^{90}Y radioembolization for chemorefractory liver metastases reported a hepatic progression–free survival of 3.0 mo for patients with colorectal metastases. Median overall survival was 8.8 mo for all patients with metastatic colorectal cancer and increased to 10.5 mo for patients with liver-only colorectal metastases (*22*).

However, most of the published literature on ^{90}Y radioembolization for colorectal liver metastases has reported on resin microspheres, in part because of differences in the approved indications for glass and resin microspheres (*20,21,23,24*). Nonetheless, a significant number of patients undergo ^{90}Y radioembolization of colorectal liver metastases with glass microspheres. The results of this multiinstitutional review of 531 patients with colorectal liver metastases treated with ^{90}Y radioembolization using glass microspheres underscore the consistent, reproducible, and favorable survival outcomes of the therapy in the salvage setting. The data show that radioembolization using glass microspheres provides reliable dose delivery and is safe and well tolerated.

Once colorectal liver metastases become chemorefractory, patients' median overall survival approaches 4–5 mo (*15–17*). In addition to the studies cited previously, several large cohort studies have reported survival data for patients undergoing salvage ^{90}Y radioembolization. These data are remarkably consistent and nearly identical to our own findings. Median overall survival from the first ^{90}Y treatment in our cohort was 10.6 mo. In the next largest published study, of 302 patients with chemorefractory colorectal liver metastases treated using resin microspheres, Saxena et al. (*1*) found a median overall survival of 10.5 mo after the first ^{90}Y treatment, which mirrors the 10.6-mo median overall survival of 214 patients treated with glass microspheres reported by Lewandowski et al. (*2*). Kennedy et al. (*3*) also reported a median overall survival of 10.5 mo among responders in a multiinstitutional review of 208 patients treated with resin ^{90}Y microspheres. Although the 214 patients reported by Lewandowski et al. were included in our multiinstitutional cohort, removal of these 214 patients from the survival analysis still indicates a median overall survival of 10.5 mo for the remaining 317 patients.

The significance of these survival outcomes in the salvage setting should not be overlooked. Although data from retrospective review certainly cannot be equated with data from prospective, randomized trials, these results resonate favorably considering the median overall survival outcomes achieved in the salvage setting with other agents. Cetuximab demonstrated a median overall survival of 9.5 mo in the salvage setting for patients with the wild-type KRAS gene, compared with 4.8 mo achieved with best supportive care (*16*). Subsequent trials investigating its use earlier in the treatment of metastatic colorectal cancer have led to its acceptance as a cornerstone of colorectal cancer treatment (*18,25*). More recently, regorafenib has become standard-of-care treatment for chemorefractory colorectal

TABLE 6
Survival by Exposure to Cytotoxic Agents (5-Fluorouracil, Oxaliplatin, or Irinotecan)

Interval (mo)	Median		*P*
	≤2 drugs	All 3 drugs	
From diagnosis of primary	49.4 (40.1–58.7) (n = 222)	47.5 (42.2–52.8) (n = 293)	0.20
From diagnosis of hepatic metastases	37.2 (31.4–43.0) (n = 222)	39.8 (35.5–44.1) (n = 294)	0.36
From first ^{90}Y treatment	14.7 (12.9–16.5) (n = 231)	9.2 (7.8–10.6) (n = 295)	<0.001
From hepatic metastases to ^{90}Y	10.9 (9.9–11.9) (n = 222)	22.6 (20.5–24.7) (n = 294)	<0.001
From ^{90}Y (no extrahepatic metastases)	16.5 (11.92–21.1) (n = 160)	13.1 (10.0–16.2) (n = 164)	0.007
From ^{90}Y (with extrahepatic metastases)	9.6 (4.7–14.5) (n = 71)	5.4 (3.9–7.0) (n = 131)	≤0.003

Ranges in parentheses are 95% CI.

TABLE 7
Survival by Exposure to Biologic Agents (Bevacizumab, Cetuximab, Panitumumab, or Regorafenib)

Interval (mo)	Median			*P*
	None	Received 1	Received 2	
From diagnosis of primary	48.9 (35.4–62.4) (n = 110)	49.4 (43.1–55.7) (n = 287)	47.5 (39.2–55.8) (n = 117)	0.98
From diagnosis of hepatic metastases	33.2 (27.5–38.9) (n = 111)	37.6 (33.3–41.9) (n = 288)	42.0 (34.8–49.2) (n = 117)	0.30
From first ^{90}Y treatment	11.5 (6.3–16.7) (n = 114)	12.9 (11.0–14.9) (n = 295)	7.0 (4.9–9.1) (n = 117)	0.001
From hepatic metastases to ^{90}Y	11.1 (8.0–14.2) (n = 111)	15.4 (13.4–17.4) (n = 288)	27.6 (24.7–30.5) (n = 117)	<0.001
From ^{90}Y (no extrahepatic metastases)	14.7 (8.7–20.8) (n = 90)	15.4 (11.0–19.8) (n = 178)	9.6 (5.8–13.4) (n = 57)	0.113
From ^{90}Y (with extrahepatic metastases)	7.6 (1.1–14.1) (n = 24)	7.8 (6.2–9.4) (n = 117)	4.5 (2.7–6.3) (n = 60)	0.113

Ranges in parentheses are 95% CI.

liver metastases by demonstrating a prolongation in median overall survival from 5 mo with best supportive care and placebo to 6.4 mo with best supportive care and regorafenib (*15*). Several prospective, randomized trials are currently evaluating the role of ^{90}Y radioembolization at different points in the treatment of colorectal liver metastases, including the EPOCH trial (*26*) and the combined 1,100-patient SIRFLOX (*27*), FOXFIRE (*28*), and FOXFIRE global (*29*) studies.

The precise and reliable dose delivery achieved with glass ^{90}Y microspheres is a critical observation. Glass microspheres have a low embolic load, which does not limit delivery of the prescribed activity of ^{90}Y (*30*). In our cohort, delivery of at least 90% of the dose was achieved in all cases. The heavy embolic load of resin microspheres, on the other hand, can result in arterial stasis, limiting the actual ^{90}Y dose delivered. In a recent phase I trial of resin microspheres for treatment of colorectal metastases, arterial stasis that limited the total administered activity occurred in 37.5% of treatment sessions (*31*). Such reliability of dose delivery with glass microspheres not only is a vital component of consistent and reproducible brachytherapeutic treatments but also is central to the principles of oncologic clinical trials, as the safety and effectiveness of a therapy cannot be evaluated if the actual dose delivered varies. This principle was confirmed in a recent phase I study of the radiosensitizing chemotherapy capecitabine used with escalating whole-liver doses of ^{90}Y glass microspheres and controlled, predictable escalation of the ^{90}Y dose (*32*). During the same period, a phase I study of resin ^{90}Y radioembolization with capecitabine therapy was published, but the ^{90}Y dose could not be escalated because dose delivery with resin microspheres is particularly unpredictable in the salvage setting for colorectal liver metastases, in which vessels can be adversely affected by chemotherapy exposure. In addition, only 41.7% of patients received whole-liver radioembolization, limiting assessment of the true liver tolerance to radioembolization during concomitant radiosensitizing chemotherapy.

Given the changes in hepatic vasculature and flow dynamics seen in patients who have been heavily pretreated with chemotherapy and biologic agents, the high activity and low embolic load of glass microspheres offer tremendous value. A frequent criticism of ^{90}Y radioembolization is the need for complex coil embolization of extrahepatic vessels in order to prevent nontarget ^{90}Y radioembolization, or the need for coil embolization of hepatic vasculature for intrahepatic flow redistribution in order to achieve dose delivery, both of which not only prolong the procedures but also carry a risk of promoting tumor-perfusing collateral artery networks—potentially complicating future treatments. In

TABLE 8
Survival by Era

Interval (mo)	Median		*P*
	Before 2004	After 2004	
From diagnosis of primary	33.3 (31.8–34.8) (n = 14)	49.4 (44.8–54.0) (n = 505)	≤0.003
From diagnosis of hepatic metastases	33.2 (17.6–48.8) (n = 14)	38.7 (35.0–42.4) (n = 507)	0.041
From first ^{90}Y treatment	7.0 (4.1–9.9) (n = 14)	10.9 (9.0–12.8) (n = 517)	0.06
From hepatic metastases to ^{90}Y	12.7 (10.0–15.5) (n = 14)	17.6 (15.5–19.7) (n = 507)	0.37
From ^{90}Y (no extrahepatic metastases)	7.0 (0.0–15.5) (n = 9)	14.7 (13.0–16.4) (n = 320)	0.12
From ^{90}Y (with extrahepatic metastases)	4.3 (1.9–6.8) (n = 5)	6.8 (5.2–8.4) (n = 197)	0.13

Ranges in parentheses are 95% CI.

TABLE 9
Multivariate Analysis for Survival

Category	Hazard ratio	*P*
Bilirubin < 1.3 mg/dL	1.23 (0.80–1.87)	0.349
Albumin > 3 g/dL	0.47 (0.35–0.63)	<0.001
ECOG 0	0.60 (0.46–0.79)	<0.001
≤2 cytotoxic agents	0.61 (0.46–0.79)	<0.001
No biologics	0.93 (0.68–1.28)	0.663
Tumor burden ≤ 25%	0.37 (0.28–0.49)	<0.001
Extrahepatic disease absent	0.50 (0.38–0.64)	<0.001
Stage IV* at diagnosis	0.88 (0.69–1.13)	0.33

*American Joint Committee on Cancer criteria.
Ranges in parentheses are 95% CI.

our cohort, however, only 25% of patients underwent arterial coil embolization, which is in line with the increasingly low rates of extrahepatic arterial embolization during glass microsphere radioembolization previously reported by our group (*33*). In our group's more contemporary patient population, prophylactic coil embolization approaches 10%. The safety of this practice is underscored by the fact that no gastrointestinal ulcers were reported.

The low rate of clinical side effects and biochemical toxicity in this large patient cohort confirms the safety of ^{90}Y when performed across institutions. The most common clinical side effects—fatigue, abdominal pain or discomfort, and nausea—were comparable to the known and expected side effects of radioembolization. Grade 3 and 4 biochemical toxicity after radioembolization affected only a minority of patients and may in fact have been overestimated in this series, which, by recording hepatic toxicity at any time after radioembolization, inevitably also captured the effects of hepatic decompensation related to tumor progression.

This study had limitations. Retrospective data collection limits the accuracy of patient-subgroup comparisons. For this reason, our study focused on the outcomes that are least prone to misinterpretation and bias, namely survival and the safety of a treatment when performed at diverse institutions. In addition, this study was confounded by variability in the number of treatments that patients received. Also, many patients did not receive all available systemic options, for reasons including poor tolerance and KRAS mutation status. Nonetheless, despite differences in local oncology practice and in the nuances of the procedure, ^{90}Y radioembolization with glass microspheres is safe and offers consistent survival outcomes for patients with chemorefractory colorectal liver metastases.

These results add to growing evidence, now comprising more than 1,000 patients, in support of ^{90}Y for treatment of colorectal liver metastases. Collaboration among oncologists and interventional radiologists is needed to conduct the large-scale, prospective trials required to more precisely define the role of ^{90}Y radioembolization in the treatment of colorectal liver metastases.

CONCLUSION

The multiinstitutional cohort of colorectal liver metastasis patients treated with ^{90}Y glass microspheres reviewed in our study is the largest yet analyzed. Our results demonstrate promising survival outcomes that are reproducible and consistent with prior reports. Glass microspheres provide reliable and precise radiation dose delivery that is safe and well tolerated. The results of the large-scale randomized studies that are under way are awaited.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734. Ryan Hickey, Robert Lewandowski, Jean-Francois Geschwind, Siddarth Padia, Mary Mulcahy, and Riad Salem are advisors to BTG. No other potential conflict of interest relevant to this article was reported.

REFERENCES

1. Saxena A, Meteling B, Kapoor J, Golani S, Morris DL, Bester L. Is yttrium-90 radioembolization a viable treatment option for unresectable, chemorefractory colorectal cancer liver metastases? A large single-center experience of 302 patients. *Ann Surg Oncol.* 2015;22:794–802.
2. Lewandowski RJ, Memon K, Mulcahy MF, et al. Twelve-year experience of radioembolization for colorectal hepatic metastases in 214 patients: survival by era and chemotherapy. *Eur J Nucl Med Mol Imaging.* 2014;41:1861–1869.
3. Kennedy AS, Coldwell D, Nutting C, et al. Resin ^{90}Y-microsphere brachytherapy for unresectable colorectal liver metastases: modern USA experience. *Int J Radiat Oncol Biol Phys.* 2006;65:412–425.
4. Salem R, Lewandowski RJ, Gates VL, et al. Research reporting standards for radioembolization of hepatic malignancies. *J Vasc Interv Radiol.* 2011;22:265–278.
5. Lewandowski RJ, Sato KT, Atassi B, et al. Radioembolization with ^{90}Y microspheres: angiographic and technical considerations. *Cardiovasc Intervent Radiol.* 2007;30:571–592.
6. Salem R, Thurston KG. Radioembolization with ^{90}Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies—part 1: technical and methodologic considerations. *J Vasc Interv Radiol.* 2006;17:1251–1278.
7. Salem R, Thurston KG. Radioembolization with ^{90}Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies—part 2: special topics. *J Vasc Interv Radiol.* 2006;17:1425–1439.
8. Salem R, Thurston KG. Radioembolization with yttrium-90 microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies—part 3: comprehensive literature review and future direction. *J Vasc Interv Radiol.* 2006;17:1571–1593.
9. Salem R, Lewandowski RJ, Sato KT, et al. Technical aspects of radioembolization with ^{90}Y microspheres. *Tech Vasc Interv Radiol.* 2007;10:12–29.
10. Salem R, Thurston KG, Carr BI, Goin JE, Geschwind JF. Yttrium-90 microspheres: radiation therapy for unresectable liver cancer. *J Vasc Interv Radiol.* 2002;13(suppl):S223–S229.
11. Ho S, Lau WY, Leung TW, Chan M, Johnson PJ, Li AK. Clinical evaluation of the partition model for estimating radiation doses from yttrium-90 microspheres in the treatment of hepatic cancer. *Eur J Nucl Med.* 1997;24:293–298.
12. Lau WY, Ho S, Leung TW, et al. Selective internal radiation therapy for nonresectable hepatocellular carcinoma with intraarterial infusion of ^{90}yttrium microspheres. *Int J Radiat Oncol Biol Phys.* 1998;40:583–592.
13. Venook APND, Lenz H, Innocenti F, et al. CALGB/SWOG 80405: phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with KRAS wild-type (wt) untreated metastatic adenocarcinoma of the colon or rectum (MCRC). Presented at: ASCO annual meeting; Chicago, IL; 2014.
14. Lenz HND, Innocenti F, Blanke C, et al. CALGB/SWOG 80405: phase III trial of irinotecan/5-FU/leucovorin (FOLFIRI) or oxaliplatin/5-FU/leucovorin (mFOLFOX6) with bevacizumab (BV) or cetuximab (CET) for patients (pts) with expanded ras analyses untreated metastatic adenocarcinoma of the colon or rectum (MCRC). Presented at: ESMO meeting; Madrid, Spain; 2014.
15. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet.* 2013;381:303–312.
16. Karapetis CS, Khambata-Ford S, Jonker DJ, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med.* 2008;359:1757–1765.
17. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. *N Engl J Med.* 2007;357:2040–2048.

18. Van Cutsem E, Cervantes A, Nordlinger B, Arnold D, Group EGW. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2014;25(suppl 3):iii1–iii9.
19. Van Hazel G, Blackwell A, Anderson J, et al. Randomised phase 2 trial of SIR-Spheres plus fluorouracil/leucovorin chemotherapy versus fluorouracil/leucovorin chemotherapy alone in advanced colorectal cancer. *J Surg Oncol.* 2004;88:78–85.
20. Hendlisz A, Van den Eynde M, Peeters M, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. *J Clin Oncol.* 2010;28:3687–3694.
21. Seidensticker R, Denecke T, Kraus P, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. *Cardiovasc Intervent Radiol.* 2012;35:1066–1073.
22. Benson AB III, Geschwind JF, Mulcahy MF, et al. Radioembolisation for liver metastases: results from a prospective 151 patient multi-institutional phase II study. *Eur J Cancer.* 2013;49:3122–3130.
23. Home page. SIRTeX.com website. http://www.sirtex.com. Accessed January 28, 2016.
24. About TheraSphere. TheraSphere.com website. http://www.therasphere.com. Accessed January 28, 2016.
25. NCCN clinical practice guidelines in oncology: colon cancer, version 2.2015. National Comprehensive Cancer Network website. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp. Accessed January 28, 2016.
26. Welcome to the enhanced peri-operative care for high-risk patients (EPOCH) trial site. Epochtrial.org website. http://www.epochtrial.org/epoch.php. Accessed January 28, 2016.
27. FOLFOX plus SIR-SPHERES MICROSPHERES versus FOLFOX alone in patients with liver mets from primary colorectal cancer (SIRFLOX). ClinicalTrials.gov website. https://clinicaltrials.gov/ct2/show/NCT00724503. Accessed January 28, 2016.
28. FOXFIRE: an open-label randomised phase III trial of 5-Fluorouracil, OXaliplatin and Folinic acid +/− Interventional Radio-Embolisation as first line treatment for patients with unresectable liver-only or liver-predominant metastatic colorectal cancer. ISRCTN registry website. http://www.controlled-trials.com/ISRCTN83867919. Accessed January 28, 2016.
29. Study design. Foxfire Global website. http://foxfireglobal.sirtex.com/study-design. Accessed January 28, 2016.
30. Sato K, Lewandowski RJ, Bui JT, et al. Treatment of unresectable primary and metastatic liver cancer with yttrium-90 microspheres (TheraSphere): assessment of hepatic arterial embolization. *Cardiovasc Intervent Radiol.* 2006;29:522–529.
31. Sofocleous CT, Garcia AR, Pandit-Taskar N, et al. Phase I trial of selective internal radiation therapy for chemorefractory colorectal cancer liver metastases progressing after hepatic arterial pump and systemic chemotherapy. *Clin Colorectal Cancer.* 2014;13:27–36.
32. Hickey R, Mulcahy MF, Lewandowski RJ, et al. Chemoradiation of hepatic malignancies: prospective, phase 1 study of full-dose capecitabine with escalating doses of yttrium-90 radioembolization. *Int J Radiat Oncol Biol Phys.* 2014;88:1025–1031.
33. Hamoui N, Minocha J, Memon K, et al. Prophylactic embolization of the gastroduodenal and right gastric arteries is not routinely necessary before radioembolization with glass microspheres. *J Vasc Interv Radiol.* 2013;24:1743–1745.