Original Article

Radioembolization of Colorectal Hepatic Metastases Using Yttrium-90 Microspheres

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BACKGROUND: The objective of the current study was to determine the safety and efficacy of Yttrium-90 (Y90) microsphere treatment in patients with liver-dominant colorectal metastases. **METHODS:** Seventy-two patients with unresectable hepatic colorectal metastases were treated at a targeted absorbed dose of 120 Gray (Gy). Safety and toxicity were assessed using version 3 of the National Cancer Institute Common Terminology Criteria. Response was assessed by anatomic imaging and positron emission tomography (PET). Survival from the diagnosis of hepatic metastases and first treatment were estimated using the Kaplan-Meier method. Substratification analyses were performed. **RESULTS:** The median dose delivered was 118 Gy. Treatment-related toxicities included fatigue (61%), nausea (21%), and abdominal pain (25%). Grade 3 and 4 bilirubin toxicities were observed in 9 of 72 patients (12.6%). The tumor response rate was 40.3%. The median time to hepatic progression was 15.4 months, and the median response duration was 15 months. The PET response rate was 77%. Overall survival from the first Y90 treatment was 14.5 months. Tumor replacement ($\leq$25% vs $>$25%) was associated with significantly greater median survival (18.7 months vs 5.2 months). The presence of extrahepatic disease was associated negatively with overall survival (7.9 months vs 21 months). Overall survival from the date of initial hepatic metastases was 34.6 months. A subset analysis of patients who had an Eastern Cooperative Oncology Group performance status of 0 demonstrated a median survival of 42.8 months and 23.5 months from the time of hepatic metastases and Y90 treatment, respectively. **CONCLUSIONS:** Y90 liver therapy appears to provide sustained disease stabilization with acceptable toxicity. Asymptomatic patients with preserved liver function at the time of Y90 appeared to benefit most from treatment. **Cancer 2009;115:1849–58. © 2009 American Cancer Society.**

KEY WORDS: ^{18}[F]fluorodeoxyglucose-positron emission tomography, hepatic arterial infusion chemotherapy, radiofrequency ablation, systemic agents, time to hepatic progression, transarterial chemoembolization, yttrium-90, TheraSphere, radioembolization, internal radiation.

Colorectal cancer (CRC) is the third most common cancer diagnosed among both men and women in the US. The American Cancer Society estimates that approximately 112,340 new cases of colon cancer (55,290 men and 57,050 women) and 41,420 new cases of rectal cancer (23,840 men and 17,580 women)

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Received: July 22, 2008; **Revised:** November 22, 2008; **Accepted:** November 26, 2008

Published online: March 6, 2009 © 2009 American Cancer Society

DOI: 10.1002/cncr.24224, www.interscience.wiley.com

were diagnosed in 2007.[1] Because the liver is the most frequent site of metastases, an estimated 60% of patients who are diagnosed with CRC eventually will experience liver disease as a predominate site.[2] Thus, unresectable liver metastases continue to account for much of the morbidity and mortality in patients with CRC.[3,4] Surgical resection of liver-confined disease for patients with no evidence of disseminated disease, a resection strategy encompassing all liver disease with adequate remnant liver for recovery and medical fitness for laparotomy, is associated with a median overall survival of 44 months and a 5-year survival rate of 35%.[5] Less than 20% of patients have liver metastases amenable to resection, a rate that may improve with current chemotherapy.[6,7] For the majority of patients without resectable disease, the median overall survival is 22 months and rarely is associated with survival beyond 5 years.[8] Targeted nonsurgical approaches for liver-confined CRC metastases may offer survival advantages beyond that of systemic therapy alone.

Numerous liver-directed therapies are available for treating unresectable liver metastases, including conformal radiation, radioembolization with yttrium-90 microspheres (Y90), hepatic arterial infusion chemotherapy (HAC) with floxuridine (FUDR), transarterial chemoembolization, or radiofrequency ablation (RFA). These treatments are being studied with and without standard therapies, including fluoropyrimidines, irinotecan, oxaliplatin, tyrosine kinase inhibitors, and vascular endothelial growth factor- and epidermal growth factor-targeting agents.[1,2,9-17] The objective of the current study was to present safety and efficacy outcomes in patients with liver-dominant colorectal metastases who were treated with hepatic-directed Y90.

MATERIALS AND METHODS

Eligibility Criteria

Seventy-two patients who presented with liver-dominant hepatic colorectal metastases were enrolled in this open-label, expanded-use protocol between 2003 and 2007. The Institutional Review Board approved the study, and all patients signed an informed consent before enrolling. Protocol entry criteria included: 1) unresectable CRC within the liver, as determined by a multidisciplinary team; 2) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) from 0 to 2; 3) the ability to undergo angiography and selective visceral catheterization; and 4) adequate hematology (granulocyte count $\geq 1.5 \times 10^9$/L, platelets $\geq 50 \times 10^9$/L), renal function (creatinine ≤ 2.0 mg/dL), and liver function (bilirubin ≤ 2.0 mg/dL). The factors that were assessed in determining unresectability included the presence or absence of extrahepatic metastases, liver function tests, tumor distribution/size, and medical comorbidities. Exclusion criteria included: 1) significant extrahepatic disease (life expectancy <3 months), 2) evidence of any uncorrectable flow to the gastrointestinal (GI) tract observed on angiography or technetium-99m macroaggregated albumin scan (^{99m}Tc-MAA), 3) the possibility that an estimated >30 Gray (Gy) would be delivered to the lungs in a single administration, and 4) concurrent chemotherapy or radiotherapy. Patients were not excluded based on perceived imaging or angiographic hypovascularity of metastatic lesions.

Patient Evaluation and Workup

After obtaining baseline laboratory tests and clinical history, patients underwent a pretreatment angiogram with selective visceral catheterization. The angiogram was conducted to assess hepatic vasculature, to determine the appropriate position of catheter placement treatment, and to identify any collateral vessels that would result in inadvertent Y90 deposition to the GI tract. To mitigate this possibility, the gastroduodenal, right gastric, or other nontarget arteries were embolized prophylactically when necessary. No patient was excluded from therapy as a result of uncorrectable collateral flow. Then, a ^{99m}Tc-MAA scan was performed to detect any unobserved GI flow and to estimate the percentage of injected activity that may shunt to the lungs.[9-11] Embolization of vessels to create flow redistribution was not performed in any patient (except for embolization of the accessory right or left hepatic arteries to redistribute flow).

Treatment Plan

The Y90 device (TheraSphere-MDS; Nordion, Ottawa, Ontario, Canada) consists of nonbiodegradable microspheres in which yttrium is an integral constituent of the glass to prevent breakdown or leaching. Ninety-five

percent of the spheres range in greatest dimension between 15 μm and 35 μm. ^{90}Y is a pure beta emitter and decays to stable ^{90}Zr with a physical half-life of 64.1 hours. The mean tissue penetration of beta is 2.5 mm (maximum, 10 mm). The method of calculating the required activity for injection and the actual dose delivered to the liver and lungs has been published previously.[12-14] In this study, the target tissue dose was 120 Gy.

Depending on disease presentation, patients received treatment on a lobar basis at 4- to 6-week intervals. A baseline computed tomography scan was conducted within 4 weeks of treatment. Baseline ^{18}[F]fluorodeoxyglucose-positron emission tomography (FDG-PET) imaging was encouraged but not mandated. Baseline symptoms and laboratory studies, including appropriate tumor markers, were obtained on the day of treatment. Patients were evaluated after each infusion at 2 weeks (by telephone) for clinical toxicity, at 4 weeks (by clinical examination, laboratory tests, and imaging studies) for toxicity and response to therapy, and every 3 months thereafter. For those patients who received bilobar treatment, a computed tomography scan was repeated just before the second lobar treatment to establish the baseline tumor size of the untreated lobe. A 3-month follow-up ^{18}FDG-PET image also was obtained in patients who had a baseline FDG-PET study. Adverse events were reported using the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0) grading classification (CTC). All toxicities that occurred anytime after treatment without time cutoff or attribution were reported. All patients were prescribed a 2-week course of proton-pump inhibitors after treatment.

Data Collection and Outcome Measures

All data were collected prospectively. Previous chemotherapy was classified by exposure to 1 or more regimens of 5-fluorouracil (5-FU), irinotecan, and oxaliplatin. Tumor response (limited to the assessment of hepatic lesions) was performed at 1 month after initial treatment and subsequently every 3 months routinely. World Health Organization (WHO) tumor response on imaging studies was determined for measurable lesions (>1 cm) by using the cross-product of perpendicular dimensions. A "complete response" was defined as a change in the sum of the cross-products to zero (ie, a 100% reduction), a "partial response" was defined as a decrease in the sum of cross-products by $\geq$50%, "stable disease" was defined as a decrease in the sum of cross-products by <50% or an increase <25%, and "progression" was defined as an increase in the sum of cross-products by $\geq$25%. The time to hepatic progression (TTHP) was defined as the time of first treatment to documentation of hepatic tumor progression beyond best response. Duration of response was defined as the time from partial response to hepatic progression. In an exploratory analysis, PET response for each lesion was classified visually by the decrease in FDG uptake into 4 categories: complete resolution, improvement, stable disease, or progression. Data were censored on December 30, 2007. For the purposes of survival analyses, patients were classified as "responders" if they met partial response criteria according to the WHO or if they had improvement on PET studies.

Statistical Analyses

Median values were used to characterize the doses delivered to the liver target. Patients who received >1 treatment to a liver segment were tabulated cumulatively. The lung dose (in Gy) was accumulated over treatments based on the percentage of activity estimated to flow to the lungs on ^{99m}Tc-MAA.

Survival analyses and substratification were conducted for all 72 patients who were enrolled in the study from the time of the initial CRC diagnosis, diagnosis of hepatic metastases, and Y90 treatment until death or last follow-up. The median survival and corresponding 95% confidence intervals (95% CIs) were computed using the method of Kaplan and Meier.[15] The log-rank test was used to test for significance obtained during subset analyses, and P values <.05 were considered significant.[15]

RESULTS

Patient Population

All 72 patients were evaluable for response, toxicity, and survival. Table 1 lists the demographic characteristics at the time of Y90 treatment. The median age was 61 years (range, 54-86 years), and most patients were men (65%) with an ECOG PS of 0 or 1 (89%). At the time of

Table 1. Patient Baseline Characteristics

Demographics	No. of Patients (%)
Age, y	
<65	41 (57)
≥65	31 (43)
Sex	
Men	47 (65)
Women	25 (35)
Ethnicity	
White	66 (92)
African American	4 (6)
Asian	2 (2)
ECOG performance status*	
0	48 (67)
1	16 (22)
2	8 (11)
Stage at CRC diagnosis	
2	10 (14)
3	17 (24)
4	45 (62)
Tumor characteristics	
Extrahepatic metastases	
Yes	29 (40)
No	43 (60)
Tumor location	
Bilobar	60 (83)
Unilobar	12 (17)
Liver replacement, %	
≤25	58 (78)
26-50	11 (19)
>50	3 (3)
Laboratory data	
AST/ALT	
≤ULN†	45 (63)
>ULN	27 (37)
Total bilirubin, mg/dL	
≤ULN	65 (90)
>ULN	7 (10)

ECOG indicates Eastern Cooperative Oncology Group; CRC, colorectal carcinoma; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper limit of normal.

* A performance status of 0 indicates asymptomatic and fully active, 1, symptomatic, fully ambulatory, restricted in physically strenuous activity; 2, symptomatic, ambulatory, capable of self-care, >50% of waking hours are spent out of bed.

† The normal level is 1.3 mg/dL.

diagnosis, 38% of patients had stage II/III disease, and 62% had stage IV disease. At the time of Y90 treatment, the majority of patients had liver-only disease (n = 43; 60%). Of the 29 patients (40%) who had minimal extrahepatic metastases, the sites of disease included lung (18%), the lymph nodes (21%), and the peritoneal lining (11%). Sixty patients (83%) had bilobar disease, and 58 patients (78%) presented with ≤25% tumor burden. Elevated bilirubin levels (above normal) were present in 7 patients (10%). The cohort's complete history of systemic agents is illustrated in Figure 1. Sixty-seven patients (93%) had received 5-FU, 51 patients (72%) had received oxaliplatin, and 35 patients (49%) had received irinotecan. Bevacizumab and cetuximab had been given to 33 patients (46%) and 12 patients (17%), respectively. The number of chemotherapy drugs patients were exposed to before Y90 therapy was 3 drugs for 28 patients (38%), 2 drugs for 30 patients (42%), and 1 drug for 10 patients (14%). Four patients (6%) who had liver-only metastases declined first-line systemic therapy and were treated with Y90. The mean time from initial CRC diagnosis to liver metastases was 7.5 months (range 0-49.7 months).

Yttrium 90 Treatment

A treatment summary is presented in Table 2. Seventy-two patients received 136 outpatient treatments (1.9 treatments per patient; range, 1-3 treatments per patient), and all patients were discharged on the same day. The median dose delivered to the liver was 118 Gy. The median lung dose per treatment was 3.2 Gy (95% CI, 2.7-3.9 Gy), and the median cumulative lung dose was 6.9 Gy (95% CI, 4.9-8.5 Gy). The median injected activity was 2.37 gigabecquerels (range, 0.67-6.57 gigabecquerels). There were no misadministrations. Prophylactic coil embolization of a nontarget vessel was necessary in 47 patients (65%).

Treatment Toxicities

Table 3 lists clinical and biochemical toxicities. Grade 1 or 2 treatment-related toxicities included fatigue that lasted 7 to 10 days in 44 patients (61%), nausea in 15 patients (21%), and abdominal pain in 18 patients (25%). There was 1 episode of a GI ulcer in a patient who had an unrecognized supraduodenal artery that responded to conservative management. In total, 9 patients (12.6%) were classified with grade 3 or 4 bilirubin toxicity, as defined by the CTC (2 patients within 3 months, 3 patients during months 3-6, and 4 patients >6 months after treatment). Reasons for post-treatment hyperbilirubinemia included tumor progression and/or biliary obstruction

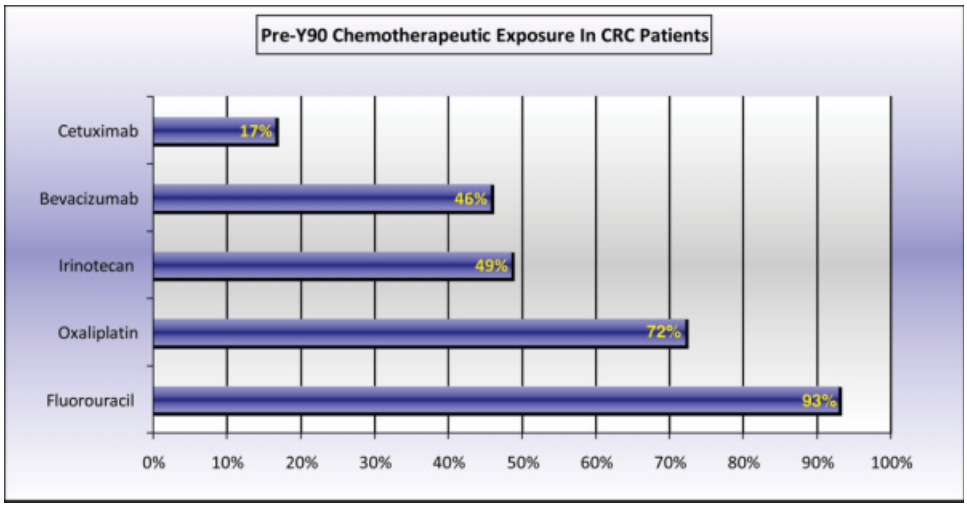

FIGURE 1. This chart illustrates exposure to systemic agents. Pre-Y90 indicates before treatment with yttrium-90 microspheres; CRC, colorectal cancer.

Table 2. Dosimetry

Location	No. of Treatments	Median Dose (95% CI), Gy	Mean Dose (95% CI), Gy
Liver	136	118 (113-123)	120 (113-125)
Lung, per treatment	136	3.2 (2.7-3.9)	4.9 (4.0-5.7)
Lung, cumulative	72	6.9 (4.9-8.5)	9.0 (6.9-11.1)

95% CI indicates 95% confidence interval; Gy, Gray.

Table 3. Clinical and Biochemical Toxicities

Adverse Event	No. of Patients	%
Clinical toxicities (grade 1/2)*		
Fatigue	44	61
Abdominal pain	18	25
Nausea	15	21
Fever	4	6
Anorexia	3	4
Diarrhea	3	4
Weight loss	2	3
Gastrointestinal ulceration	1	1
Biochemical toxicities (grade 3/4)†		
Bilirubin	9	13
Alkaline phosphatase	6	8
ALT/AST	4	6

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase.
* Listed are toxicities that occurred postprocedurally.
† Listed are toxicities that were reported anytime during follow-up.

from extrahepatic lymphadenopathy. Of the 7 patients who had had elevated bilirubin levels (>1.3 mg/dL) at baseline, the following bilirubin toxicities were noted after treatment: grade 1→0 (1 patient), grade 1→1 (1 patient), grade 1→2 (2 patients), grade 1→4 (1 patient), grade 2→2 (1 patient), and grade 2→3 (1 patient). There were no 30-day mortalities or episodes of radiation pneumonitis.

Tumor Response

One hundred twenty-eight target lesions were used to determine response, TTHP, and duration of response. A partial response according to WHO criteria was noted in 29 of 72 patients (40.3%). At the lesional level, the response rate was 40.6% (partial response rate, 37.5%; complete response rate, 3.1%), stable disease was observed in 44.5% of patients, and disease progression was observed 14.8% of patients. The median time to partial response was 4 months (95% CI, 2.8-4.5 months), the median TTHP was 15.4 months (95% CI, 5.4-18 months), and the median response duration was 15 months (95% CI, 14.4-17.2 months). Improvement was noted in 30 of 39 patients (77%) who had pretreatment and post-treatment PET studies available.

Survival

Overall survival outcomes for selected prognostic variables are provided in Table 4. The median follow-up was

Table 4. Overall Survival

Category	No. of Patients	Median Survival, mo	95% CI	*P**
Survival from the date of diagnosis				
From diagnosis of CRC	72	40.3	29-51.6	
5-Y survival rate, %	72	30%	16.9%-42.3%	
CRC stage at diagnosis				
2/3	27	68.1	45-105.3	.0001
4	45	29	20.2-39.1	
Survival from the date of liver metastases				
From diagnosis of hepatic metastases	72	34.6	24.4-41.8	
5-Y survival rate, %	72	17.7%	7.3%-28%	
From diagnosis of liver metastases in patients with ECOG 0 @Y90	48	42.8	28-48.7	
5-Y survival rate in patients with ECOG 0 @Y90, %	48	28.3%	17.2%-38%	
CRC stage at diagnosis				
2/3	27	42.8	18.9-51	.1691
4	45	29.0	20.2-39.1	
Survival by liver-only metastases				
Yes	43	41.8	31.8-56.3	
No	29	24.4	16.8-35.9	
Survival from the date of first Y90 treatment				
Survival from Y90 treatment	72	14.5	9.6-21.9	
ECOG performance status				
0	48	23.5	17-31.9	<.0001
1	16	6.7	5.2-14.4	
2	8	4	1.7-7	
Bilobar disease				
Yes	60	13	8.7-18.7	.0953
No	12	23.5	12.5 to —	
Tumor replacement				
≤25%	58	18.7	12.9-32	<.0001
>25%	14	5.2	3.5-9.6	
Extrahepatic disease				
Yes	29	7.9	4.5-12.5	.0004
No	43	21	13-32	
Responders†				
Yes	39	23.5	16.8 to —	<.0001
No	33	8.5	5-14.5	
CRC stage at diagnosis				
2/3	27	23.5	— to 18.7	.0116
4	45	9.6	7-13	

95% CI indicates 95% confidence interval; CRC, colorectal carcinoma; ECOG 0 @Y90, patients with an Eastern Cooperative Oncology Group performance status of 0 who were treated with yttrium-90 microspheres.
* *P* values were determined using the log-rank test.
† Response was determined according to World Health Organization criteria or improvement on positron emission tomography studies.

26.2 months. The median survival was 40.3 months (95% CI, 29.0-51.6 months) for all patients from the time of cancer diagnosis, 34.6 months (95% CI 24.4-41.8) from the time liver metastases were diagnosed, and 14.5 months (95% CI 9.6-21.9) from the time of Y90 therapy. The 5-year survival rate was 30% (95% CI, 16.9%-42.3%) from the time of cancer diagnosis and 17.7% (95% CI, 7.3%-28%) from the time liver metastases were diagnosed. Subset analysis identified PS, tumor burden ≤25%, and the absence of extrahepatic disease as favorable predictors of survival from the time of Y90 treatment. Distribution of metastases (unilobar vs bilobar) did not predict outcome. Patients who had an ECOG PS of 0, a liver tumor burden ≤25%, and no extrahepatic disease (n = 35) had a median survival of 25.8 months (95% CI, 16.9-64.3 months) from the time of Y90 therapy. Radiographic response to therapy did predict an improved overall survival (23.5 months vs 8.5 months; $P = .0001$). The

Table 5. Survival by Chemotherapy Exposure

	<3 Agents, N=44		≥3 Agents, N=28		
Survival	Months	95% CI	Months	95% CI	*P*
From date of CRC diagnosis	41.7	28.2-68.1	39.1	28.3-51.5	.1811
From date of liver metastases	35.8	22.2-66.0	34.6	24.4-45.3	.2530
From date of Y90 therapy	19.7	13 to —	9.4	7 to —	.0053

95% CI indicates 95% confidence interval; CRC, colorectal carcinoma; Y90, yttrium-90 microspheres.

median survival in the 7 patients who had elevated baseline bilirubin levels (>1.3 mg/dL) was 5.3 months (95% CI, 4.3-14.6 months).

Median survival from the time of cancer diagnosis or hepatic metastases was not affected by therapy that was received before Y90 (Table 5). For patients who had multidrug-refractory disease who had received all 3 active chemotherapy agents (5-FU, irinotecan, and oxaliplatin) before Y90 therapy, the median survival from the time of diagnosis of liver metastases was 34.6 months (95% CI, 24.4.3-45.3 months) compared with 35.8 months (95% CI, 22.2-66 months) for patients who received Y90 therapy before all 3 chemotherapy agents ($P = .2530$). From the time of Y90 therapy, patients who had received all 3 active agents had a median survival of 9.4 months compared with 19.7 months for patients who still had active systemic therapy options available.

DISCUSSION

CRC continues to have high mortality rates despite the introduction of several new systemic agents, combinations, and methods of administration.[16-18] A paradigm shift has been proposed that abandons the concept of lines of therapy and embraces an individualized continuum of care.[8] The goals of this approach are to maximize survival and quality of life while minimizing toxicity. Strategies to accomplish this include incorporating changes in chemotherapy before progression, the use of maintenance therapy, taking drug holidays, and pursuing surgical resection of metastases in selected patients. Although surgical resection of liver metastases is available to <20% of patients, alternative approaches to treating liver-confined disease with acceptable toxicity may expand this paradigm. The data presented here provide evidence of the safety and efficacy of Y90 for colorectal liver metastases within the paradigm of continuum of care.

Y90 is a brachytherapy treatment option that can be administered by intra-arterial hepatic injection. Metastatic tumors receive the majority of their blood supply from the hepatic artery as opposed to liver parenchyma (portal vein blood supply). Consequently, intra-arterial Y90 can deliver high radiation doses to tumor while sparing liver parenchyma, resulting in tumoricidal effects with minimal liver toxicity.[12]

In the current study, we observed that the safety profile of this therapy was acceptable. Clinical toxicities usually were transient and consisted mainly of grade 1 and 2 fatigue and abdominal pain that did not require analgesics. Conservatively, grade 3 and 4 biochemical toxicities were reported at anytime during the patient follow-up and were not censored at any specified time. Hence, the 6% to 13% adverse event rate for patients also was deemed acceptable. These rates compare favorably with other reported cohorts who received Y90 treatment.[19-21]

Significant adverse events to Y90 therapy usually are GI in nature. This is most likely because of the inadvertent deposition of microspheres into the GI tract through unrecognized collateral vessels, leading to ulcer formation.[22] Placement of the catheter in the right or left hepatic artery distal to collateral vessels, as implemented in the current study, minimizes the likelihood of nontarget collateral flow to the GI tract. Thus, consideration should be made for prophylactic coil embolization of extrahepatic vessels before Y90 infusion to minimize the possibility of nontarget embolization.[22-24] To mitigate these risks further, all patients were treated prophylactically with proton-pump inhibitors. Despite these precautions, we did encounter 1 treatment-related gastric ulcer that responded to conservative therapy.

Technical considerations for this therapy deserve special mention. Although embolic therapies are based on the foundations of chemoembolization, this therapy is distinctly different. Y90 requires a more thorough

knowledge of vascular anatomy, infusion techniques, and embolization. Hence, analogous to surgical resection or hepatic artery pump placement, a learning curve and specialized expertise are required when applying this therapy to properly selected patients. These previously published standards were applied to our cohort.[22,23,25] Centers that use this technology are encouraged to apply these basic principles to maximize the safety profile and to optimize long-term outcomes.

The highly localized radiation effect translated to an imaging response rate of 40.6% with a corresponding TTHP of 15.4 months and a response duration of 15 months. This compares favorably to response rates with second- and third-line therapy using HAC (10%-25%), panitumumab monotherapy (7%-11%), cetuximab monotherapy (8.5-11.6%), FUDR (44%), sequential chemotherapy (the Medical Research Council Fluorouracil, Oxaliplatin, and CPT11 [irinotecan] Use and Sequencing or FOCUS trial, 11%-23%; the Capecitabine, Irinotecan, and Oxaliplatin in Advanced Colorectal Cancer of CAIRO trial, 4%-12%), and previous cohorts of Y90 (35%).[19,21,26-29] Similar to previous findings, the PET response rate in our study was 77%.[30-34]

Outcomes in this report are described from the date of diagnosis of CRC to account for differences in survival among patients who presented with stage II or III disease compared with patients who presented with stage IV disease. Survival from the date of hepatic metastases describes the outcome when Y90 is incorporated into the continuum of care, regardless of the line of therapy, and explores the influence of Y90 therapy on previous or subsequent systemic therapy. No difference in overall survival from the time of CRC diagnosis or detection of liver metastases was demonstrated when Y90 was included in the continuum of care after administration of all 3 active chemotherapy drugs or before the receipt of all 3 drugs. Using the time point from the date of Y90 therapy illustrates the response rate of the therapy and identifies predictive characteristics.

To identify baseline factors that were associated with improved outcomes, substratification analyses were performed. Favorable prognostic factors that indicated a benefit from Y90 therapy included an ECOG PS of 0, a liver tumor burden $\leq$25%, and the absence of extrahepatic disease. The distribution of liver metastases in a single liver lobe or in both lobes was not predictive of survival. In patients who had an ECOG PS of 0 at the time of Y90 treatment, the overall median survival from the onset of liver metastases was 42.8 months, which translates into a 5-year survival rate of 25.9%. These outcomes are comparable to survival data for patients who were treated with primary resection, chemotherapy followed by resection, or RFA.[4,35-37]

The current study had limitations. First, this was a single-arm, open-label study with no control arm. This was a single-center experience with significant technical and patient selection expertise. Applying proper methodology and patient selection may yield comparable outcomes. The enrollment of patients resembled actual clinical practice and was left to the discretion of physicians and patients. The majority of patients had progressed on at least 1 previous systemic therapy while maintaining liver-dominant disease. The median overall survival from the time of diagnosis of liver metastases of 34.6 months (and 42.8 months for patients with an ECOG PS of 0) may have been influenced by patient selection. By enrolling patients who were treated previously for liver-confined disease, we excluded patients who had rapid progression, which indicated either unfavorable biology or a decline in liver function. Finally, patients who had limited extrahepatic metastases were permitted to participate in the protocol, and excluding them may have enhanced survival outcomes.

In conclusion, although surgery is the only curative option for the minority of patients who present with resectable liver metastases, alternate locoregional approaches must be developed for patients who have unresectable disease. Some of these techniques are established now, including portal vein embolization (leading to resection) and RFA. Radioembolization with Y90 is an emerging outpatient treatment option that is not limited by lesion characteristics (size, shape, location, number) or patient comorbidities that would preclude RFA or surgery. Given these strict selection criteria for resection or ablative techniques, arterial therapy such as Y90 may represent an option that is applicable to the large percentage of patients who have nonablatable, nonoperable disease. In particular, patients with normal liver functions, an ECOG PS of 0, and liver-only disease appear to represent a select group that has the best long-term outcomes.

The outcomes reported herein represent evidence that nonsurgical liver-directed therapy may play a role in

the new paradigm of treatment for patients with metastatic CRC. Y90 fulfills the requirement of acceptable toxicity profile and, in carefully selected patients with unresectable liver disease, may add to active systemic therapies to improve survival and quality of life. The difference in median survival from the time of Y90 therapy in patients who had exposure to <3 systemic chemotherapy agents, compared with patients who received all 3 active agents, suggests that Y90 did not impair the ability of patients to receive subsequent active chemotherapy, resulting in equivalent overall survival. Our findings should help in clinical trial design and in identifying the optimal population and ideal time of Y90 intervention that may offer the greatest benefit. Investigations using this paradigm and combination with systemic therapy in properly selected patients are warranted.

Conflict of Interest Disclosures

Dr. Salem acts as an advisor to MDS Nordion.

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