

## 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

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### ABSTRACT

#### Purpose

Liver dissemination is a major cause of mortality among patients with advanced colorectal cancer. Hepatic intra-arterial injection of the  $\beta$ -emitting isotope yttrium-90 ( $^{90}\text{Y}$ ) bound to resin microspheres (radioembolization) delivers therapeutic radiation doses to liver metastases with minimal damage to adjacent tissues.

#### Patients and Methods

We conducted a prospective, multicenter, randomized phase III trial in patients with unresectable, chemotherapy-refractory liver-limited metastatic CRC (mCRC) comparing arm A (fluorouracil [FU] protracted intravenous infusion 300 mg/m<sup>2</sup> days 1 through 14 every 3 weeks) and arm B (radioembolization plus intravenous FU 225 mg/m<sup>2</sup> days 1 through 14 then 300 mg/m<sup>2</sup> days 1 through 14 every 3 weeks) until hepatic progression. The primary end point was time to liver progression (TTLP). Cross-over to radioembolization was permitted after progression in arm A.

#### Results

Forty-six patients were randomly assigned and 44 were eligible for analysis (arm A, n = 23; arm B, n = 21). Median follow-up was 24.8 months. Median TTLP was 2.1 and 5.5 months in arms A and B, respectively (hazard ratio [HR] = 0.38; 95% CI, 0.20 to 0.72; *P* = .003). Median time to tumor progression (TTP) was 2.1 and 4.5 months, respectively (HR = 0.51; 95% CI, 0.28 to 0.94; *P* = .03). Grade 3 or 4 toxicities were recorded in six patients after FU monotherapy and in one patient after radioembolization plus FU treatment (*P* = .10). Twenty-five of 44 patients received further treatment after progression, including 10 patients in arm A who received radioembolization. Median overall survival was 7.3 and 10.0 months in arms A and B, respectively (HR = 0.92; 95% CI, 0.47 to 1.78; *P* = .80).

#### Conclusion

Radioembolization with  $^{90}\text{Y}$ -resin microspheres plus FU is well tolerated and significantly improves TTLP and TTP compared with FU alone. This procedure is a valid therapeutic option for chemotherapy-refractory liver-limited mCRC.

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### INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide, with approximately 1 million new cases diagnosed annually.<sup>1</sup> For patients who present with metastatic CRC (mCRC), the prognosis is poor, except for a minority who are eligible for curative resection.<sup>2</sup> Chemotherapy combined with biologic agents have improved mCRC median survival rates and rendered an increasing number of patients resectable.<sup>3-10</sup> However, the recurrent nature of mCRC, particularly in the liver, remains a

life-limiting prognosis for the majority of patients with advanced disease.<sup>2,11</sup> Current tumor management relies progressively more on multimodal approaches to consolidate regional response from systemic chemotherapies and increase the number of patients who are candidates for resection.<sup>12</sup>

Radioembolization or selective internal radiation therapy with microspheres loaded with the radionuclide yttrium-90 ( $^{90}\text{Y}$ ) enables multiple hepatic metastases to be targeted in a single procedure.<sup>13</sup> The  $^{90}\text{Y}$ -resin microspheres (SIR-Spheres; Sirtex Medical, Sydney, Australia) lodge within the

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malignant microvasculature, where they deliver high, localized, therapeutic doses of  $\beta$ -radiation to tumor over approximately 14 days while maintaining radiation exposure of the normal liver within tolerable levels.<sup>14-16</sup> This procedure is increasingly being used to manage liver tumors of various histologic origins.<sup>17-19</sup>

In general, the incidence and severity of adverse events with radioembolization are low and manageable, provided that standard safety procedures are followed.<sup>13</sup> A simulation of the treatment is first performed by injecting tracer doses of technetium-99m-labeled macroaggregated albumin (<sup>99m</sup>Tc-MAA) intra-arterially with the catheter tip in the intended treatment position after meticulous angiographic interrogation of the hepatic arterial vasculature and occlusion of hepatic arterial branches that supply the gastrointestinal tract or other organs. <sup>99m</sup>Tc-MAA distribution, measured using tomographic imaging (single-photon emission computed tomography [SPECT]) coregistered with computed tomography (CT) or positron emission tomography (PET), is accepted as a good surrogate of the microspheres' distribution.<sup>20,21</sup>

Few data from randomized controlled trials on radioembolization in mCRC are published. <sup>90</sup>Y-resin microspheres have been combined with systemic chemotherapy (fluorouracil [FU]/leucovorin [LV], FOLFOX, irinotecan) or hepatic arterial infusion (HAI; floxuridine [FUDR]) for the first- or second-line treatment of CRC liver metastases.<sup>22-25</sup> In these studies, patients seemingly benefitted from an impressive tumoral response and time to progression or progression-free survival.<sup>22-25</sup> In a phase III randomized study,<sup>25</sup> 74 patients with unresectable CRC liver metastases received either HAI-FUDR with or without a single injection of <sup>90</sup>Y-resin microspheres. Patients receiving radioembolization had a significantly higher tumor response rate (44% v 18%) and lower rate of hepatic progression (8.3% v 23.5%) compared with those receiving chemotherapy alone. Toxicity (mainly elevated liver function tests and nausea) was mild in both groups. Most of the published data on salvage radioembolization in mCRC has been generated from retrospective or single-center studies.<sup>26-28</sup> Nevertheless, these reports consistently suggest the therapeutic potential of radioembolization in heavily pretreated patients with CRC liver metastases.

In this prospective multicenter randomized phase III trial, we assessed the safety and efficacy of intra-arterial <sup>90</sup>Y-resin microspheres in liver-limited mCRC among patients for whom all other evidence-based treatments had failed.

## PATIENTS AND METHODS

### Patients and Baseline Investigations

Patients with histologically proven adenocarcinoma of the colon or rectum metastasized to the liver only, not amenable to curative surgery or local ablation and resistant or intolerant to standard chemotherapy (FU, oxaliplatin, and irinotecan), were included in this trial. In case of intolerance leading to previous chemotherapy stop, documentation of progressive disease was required before study entry. Anti-epidermal growth factor receptor (EGFR) and anti-vascular endothelial growth factor therapies were routinely not available in Belgium during the trial recruitment period. Assessment of disease progression in the liver was based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0<sup>29</sup> and documented by CT or magnetic resonance imaging during or within 6 months after stopping previous therapy. Eligible patients had an Eastern Cooperative Oncology Group performance status of 0 to 2; were  $\geq 18$  years of age; had adequate bone marrow function (absolute neutrophil count  $\geq 1,000/\mu\text{L}$ , platelet count  $\geq 100,000/\mu\text{L}$ ), renal function

(creatinine  $< 1.5 \times$  upper limit of normal limit [ULN] or creatinine clearance  $> 50$  mL/min), and liver function (defined by direct bilirubin  $< 1.0 \times$  ULN; AST, ALT, and alkaline phosphatase levels each  $< 5 \times$  ULN); and were able to give informed consent.

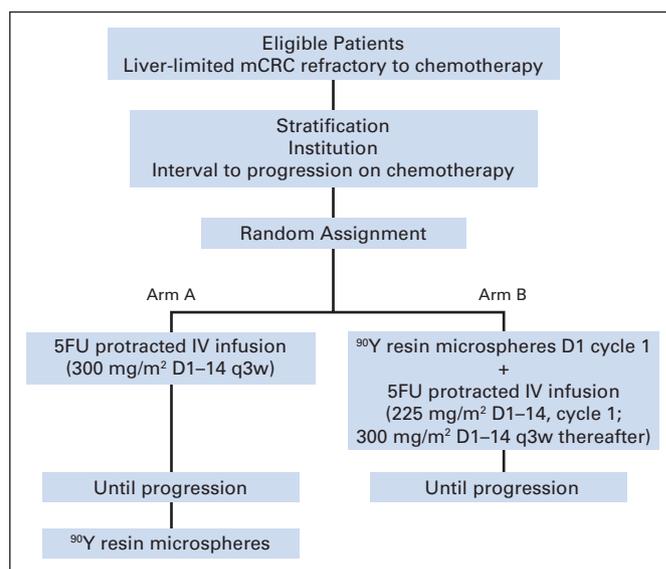
Exclusion criteria were defined as preexisting hepatic disease (cirrhosis  $>$  Child-Pugh B, liver abscess, hepatic sarcoidosis or tuberculosis, sclerosing cholangitis); extrahepatic disease; clinically significant ascites; more than 20% arteriovenous shunting from liver to lungs observed on the <sup>99m</sup>Tc-MAA scan; hepatic arterial anatomy that would not allow safe administration of <sup>90</sup>Y-microspheres; partial or total thrombosis of the hepatic artery or main portal vein; prior HAI with FU, FUDR, or other chemotherapeutic agent(s) or transarterial embolization procedure; prior external-beam irradiation of the liver; severe chronic or acute disease, concomitant or previous malignancies within 5 years other than basal cell or squamous cell carcinoma of the skin or cervix; and women who were pregnant or breast-feeding or who refused to take adequate pregnancy prevention measures.

The trial was approved by central and local ethics committees. Patients enrolled in one of three participating centers in Belgium, were fully informed of the nature of the trial and signed an informed consent.

In addition to clinical examination and blood tests (full blood count, serum renal and liver function tests, and carcinoembryonic antigen, all patients underwent contrast-enhanced CT scan, positron emission tomography with [<sup>18</sup>F]fluorodeoxyglucose (FDG-PET), hepatic arteriography, and treatment simulation with <sup>99m</sup>Tc-MAA imaging before treatment.<sup>13-15</sup>

### Study Design and Protocol Treatment

The study (Fig 1) was designed as an open-label, randomized, phase III clinical trial. Patients randomly assigned to arm A received protracted intravenous (PIV) infusion of FU 300 mg/m<sup>2</sup> days 1 through 14 every 3 weeks until progression. Patients randomly assigned to arm B received radioembolization plus intravenous FU 225 mg/m<sup>2</sup> for 14 days followed by 1 week of rest. Thereafter, patients continued with PIV FU 300 mg/m<sup>2</sup> for 14 days every 3 weeks until documented hepatic progression. For ethical reasons, patients in arm A with documented progression were permitted to cross-over to receive radioembolization at the investigators' discretion. Procedures were standardized at all participating centers. In a first investigation, a liver angiography was performed under local anesthesia to visualize tumor supply and arterial connections between the hepatic artery and the gastrointestinal tract. Potential dangerous side branches and anastomoses (ie, gastroduodenal, right gastric, supraduodenal, falciform artery) were occluded by coil embolization and lung shunt evaluated by injecting MAA into the hepatic artery in the planned



**Fig 1.** Study design. mCRC, metastatic colorectal cancer; 5FU, fluorouracil; IV, intravenous; D, day; q3w, every 3 weeks; <sup>90</sup>Y, yttrium-90.

treatment position. After exclusion of lung shunting more than 20%, therapy was organized within 14 days. In case of extrahepatic activity persistence on MAA imaging, coil embolization of the culprit artery was performed just before stepwise administration of <sup>90</sup>Y-microspheres into the hepatic artery.

The maintenance of antegrade flow was confirmed, and retrograde contamination to the gastrointestinal tract was excluded. All patients were treated only once, remained in hospital overnight, and were discharged the following day.

**Table 1.** Patient Demographics, Disease Characteristics, and Investigative Treatments

Parameter	FU Alone (n = 23)		Radioembolization + FU (n = 21)	
	No.	%	No.	%
<b>Institution</b>				
Institut Jules Bordet, ULB, Brussels	11	48	11	52
Universitair Ziekenhuis, Gent	8	35	6	29
University Hospital Gasthuisberg, Leuven	4	17	4	19
<b>Sex</b>				
Male	18	78	10	48
Female	5	22	11	52
<b>Age, years</b>				
Median	62		62	
Range	45-80		46-91	
<b>ECOG performance status</b>				
0	17	74	15	71
1	5	22	5	24
2	1	4	1	5
<b>Diagnosis</b>				
Adenocarcinoma	22	96	21	100
Adenocarcinoma mucinous	1	4	0	0
<b>Time since diagnosis, months</b>				
Median	22		22	
Range	12-44		7-52	
Missing	0	0	1	5
<b>Time since last chemotherapy, weeks</b>				
Median	14		8	
Range	2-60		2-57	
Missing	0	0	2	10
<b>Previous chemotherapy regimen*</b>				
Irinotecan based	20	87	13	62
Oxaliplatin based	2	9	4	19
Other based	1	4	4	19
<b>No. of liver metastases measured</b>				
1 lesion	1	4	2	10
2-4 lesions	10	44	10	48
≥ 5 lesions	10	44	8	38
Not measurable†	2	9	1	5
<b>Presence of nontarget lesions</b>				
Yes	6	26	5	24
Missing	1	4	1	5
<b>Sum of the lesions diameters, mm</b>				
Median	216		176.5	
Range	51-416		31-324	
Missing	2	9	1	5
<b><sup>90</sup>Y resin microspheres activity, GBq</b>				
Median	NA		1.79	
Range	NA		1.32-2.15	
Missing	NA		3	14
<b>FU dose per patient, mg</b>				
Median	17,700		14,588	
Range	3,240-119700		4,740-97,612	
Missing	3	13	1	5

Abbreviations: FU, fluorouracil; ULB, Université Libre de Bruxelles; ECOG, Eastern Cooperative Oncology Group; NA, not applicable.

\*Only data about the last chemotherapy regimen received before study entry were collected. By irinotecan-based chemotherapy regimen, we mean irinotecan ± FU ± an anti-epidermal growth factor receptor. The same applies for irinotecan- or oxaliplatin-based regimens.

†Mainly due to extensive and confluent lesions.

The administered activity of  $^{90}\text{Y}$ -microspheres was calculated according to the manufacturer's instructions based on the body-surface area and extent of tumor involvement using the following equation:

$$\text{Activity injected (GBq)} = (\text{BSA} - 0.2) + (\text{tumor volume/total liver volume}) \quad (1)$$

Activity was decreased by 20% for hepatopulmonary shunting of 10% to 15% and by 40% for shunting of 15% to 20%. Radioembolization was contraindicated for shunting more than 20%.

Chemotherapy was continued until disease progression, unacceptable toxicity, or withdrawal of consent. Adverse events were classified and coded for severity using Common Terminology Criteria for Adverse Events, version 3.0.<sup>30</sup> Physical examination and blood tests were performed every 3 weeks. CT scanning of the chest, abdomen, and pelvis was repeated every 6 weeks until disease progression. Objective tumor response was evaluated by local radiology review using RECIST 1.0.<sup>29</sup> At the investigators' discretion, radiologic tumor assessment could be repeated early on the basis of clinical need or suspicion of disease progression.

### Statistical Considerations and Statistical Analysis

The primary objective of this trial was to detect the impact of radioembolization on time to liver progression (TTLP) using a two-sided log-rank test with a significance level of .05. On the basis of previous studies, we anticipated a TTLP of 6 weeks in arm A. With an estimated 90% power, 35 progressions were required to demonstrate an increase in median TTLP from 6 to 18 weeks in arm B. Assuming a minimum follow-up time of 30 weeks, we estimated that 26 patients would be required per treatment arm to observe these progressions; however, with an estimated 10% death rate without progression, we planned to enroll 58 patients. However, accrual was lower and follow-up longer than planned, so the trial was closed with the number of enrolled patients lower than foreseen, but with the required number of progressions.

Randomization used the minimization technique, with institution and type of progression (while still receiving chemotherapy or delayed within 6 months after the cessation of chemotherapy) before enrollment as stratification factors. TTLP and TTP were calculated as the time elapsed between randomization and first documented progression in the liver or first documented progression at any site, death, or date of last observation (in patients lost to follow-up). Overall survival was defined as the time elapsed between randomization and death from any cause.

The distribution of time to event variables was estimated by the nonparametric Kaplan-Meier method. Comparison was made using the log-rank test, and treatment effect was reported by the estimation of a hazard ratio (HR) obtained with Cox regression models. The point estimates are reported with 95% CIs, and all reported *P* values are two-sided. Response rates were compared using Fisher's exact test. A *P* value was considered as significant if less than .05.

For efficacy analysis, all eligible patients were considered. For safety analysis, eligible patients not treated were excluded.

## RESULTS

### Patients

Forty-six patients (23 in each arm) were randomly assigned between December 15, 2004, and November 15, 2007, at three institutions. Two patients, both in arm B, were ineligible due to the presence of bone metastases ( $n = 1$ ) and technical issues impairing administration of  $^{90}\text{Y}$ -microspheres ( $n = 1$ ; Fig 1). Baseline and treatment characteristics and accrual by institution for the remaining 44 patients are summarized in Table 1. Both arms were well balanced for clinical criteria. The median time from diagnosis was 22 months overall. Most patients had at least two hepatic lesions. The median sum of the diameters of target lesions was 216.0 mm and 176.5 mm, respectively, in arms A and B.

**Table 2.** Best Overall Hepatic Response

Response	FU Alone (n = 23)		Radioembolization + FU (n = 21)	
	No.	%	No.	%
Partial response	0	0	2	10
Stable disease	8	35	16	76
Progressive disease	14	61	2	10
Nonevaluable	1	4	1	5

NOTE. Comparison of response rates: 0 of 23 versus two of 21,  $P = .22$  (95% CI for the difference between arms B and A ranging from  $-0.10$  to  $0.32$ ). Comparison of stabilization rates: eight of 23 versus 18 of 21,  $P = .001$  (95% CI for the difference ranging from  $0.19$  to  $0.71$ ). Abbreviation: FU, fluorouracil.

By May 1, 2008, the median follow-up was 24.8 months (range, 2 to 41 months) and 10 months for the seven patients who were still alive at the time of closure of the database.

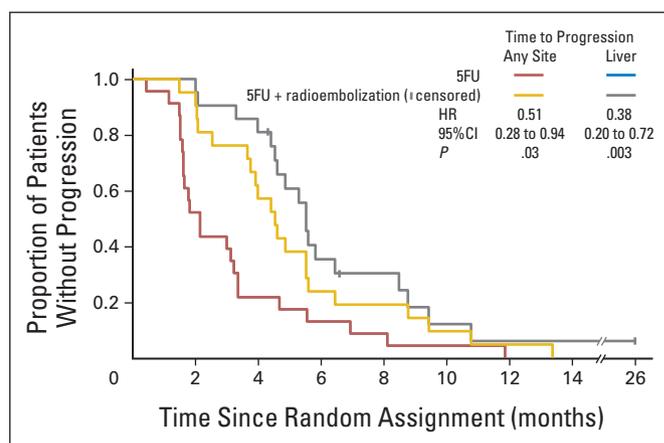
### Response Assessment

Table 2 summarizes the best overall hepatic response for target lesions according to RECIST. Overall response rates in arms A and B were 0 of 23 patients (0%) and two of 21 patients (9.5%;  $P = .22$ ), respectively, and disease control rates (partial response and stable disease) were eight (35%) of 23 patients and 18 (86%) of 21 patients ( $P = .001$ ), respectively.

### Efficacy

Liver progression was documented in 41 patients. Median TTLP in arms A and B (with 23 and 18 events, respectively) was 2.1 and 5.5 months, respectively (HR = 0.38; 95% CI, 0.20 to 0.72;  $P = .003$ ; Fig 2). Log-rank test provided a two-sided *P* value of .002. All the patients allocated to arm A experienced disease progression first in the liver. For these patients, time to liver progression equals time to progression, and therefore, two of the curves presented in Figure 2 are superimposed. Three patients in arm B were without documented progression and were censored at 4.3, 6.6, and 26.0 months.

Local progression was documented in four patients after an unjustified change in the treatment allocated by randomization. When



**Fig 2.** Time to progression in the liver (the primary end point) and at any site, taking all progressions into account. 5FU, fluorouracil; HR, hazard ratio.

**Table 3.** Time to Liver Progression, Time to Progression Overall, and Overall Survival

Time to Progression and OS	FU Alone (n = 23)	Radioembolization + FU (n = 21)	Hazard Ratio	95% CI	P
TTLP, median, months					
All progressions considered as events	2.1	5.5	0.38	0.20 to 0.72	.003
Patients with treatment change censored at the time of change	2.1	5.6	0.35	0.18 to 0.69	.002
TTP, median, months	2.1	4.5	0.51	0.28 to 0.94	.03
OS, median, months	7.3	10.0	0.92	0.47 to 1.78	.80

Abbreviations: TTLP, time to liver progression; TTP, time to progression overall; OS, overall survival; FU, fluorouracil.

these four patients were censored, the median TTLP in each arm remained unchanged, with 22 and 15 events and a two-sided *P* value of .001 (HR = 0.35; 95% CI, 0.18 to 0.69; *P* = .002). One patient in arm B with a hilus liver metastasis with suspected invasion of the right portal vein branch was sufficiently downsized for a right hepatectomy. Unfortunately, extrahepatic disease progression was documented 1.5 months after surgery. Median TTP at any site was 2.1 months in arm A and 4.5 months in arm B (HR = 0.51; 95% CI, 0.28 to 0.94; *P* = .03).

Sixteen patients randomly assigned to arm A received further therapies, including 10 patients who crossed-over to radioembolization monotherapy. The six remaining patients received cetuximab combined with chemotherapy (five patients) or chemotherapy alone (one patient). In arm B, nine patients received further systemic treatment comprising cetuximab plus chemotherapy (three patients) or chemotherapy alone (four patients); one patient received palliative brain radiotherapy and another received an unspecified treatment.

There was no significant difference in median overall survival between the treatment arms: 7.3 months for arm A (two patients alive at the time of analysis) and 10.0 months for patients in arm B (five patients alive; HR = 0.92; 95% CI, 0.47 to 1.78; *P* = .80; Table 3).

### Toxicities

Toxicity analysis was conducted in 43 patients (22 in arm A and 21 in arm B). Two patients (both in arm A) were never treated and so were not evaluated for toxicity. Grade 3 or 4 toxicities were recorded in six patients after FU monotherapy and in one patient after radioembolization plus FU treatment (*P* = .10; Table 4).

## DISCUSSION

A minority of patients (*n* = 12) enrolled in this trial had received anti-EGFR therapy previously (eight in arm A and four in arm B); most of them had received as last chemotherapy regimen irinotecan (alone or combined with FU or with anti-EGFR), including 12 patients in arm A and 17 patients in arm B. In this setting, our study shows that among patients with heavily pretreated nonresectable liver-limited mCRC, radioembolization significantly prolongs liver tumor growth control over protracted intravenous FU treatment alone and does not increase the toxicity of FU. Overall, the incidence of adverse events after radioembolization remained low and easily manageable. Reported adverse events with radioembolization (asthenia, nausea, anorexia, and abnormal liver function) were consistent with previous studies.<sup>22-28</sup> More patients experienced grade 3 toxicities in the FU-only arm. This difference was probably largely due to lower efficacy and more rapidly progressive disease in the FU arm because

the nature of the adverse events were essentially indistinguishable from those due to disease progression. The FU dose-intensity was nonsignificantly higher in arm A, which may partially explain some of the differences in toxicity between groups. No significant difference in overall survival between the two arms was observed in this study. It is likely that the rapid cross-over of 70% of patients in the FU-only arm to receive further therapy, including 10 who received radioembolization with a similar activity as arm B, confounded the survival data. We report in this study a median overall survival of 8.7 months for the entire cohort, beyond what is usually reported for an advanced chemotherapy-refractory mCRC population.<sup>31</sup> This seemingly prolonged survival could have been bolstered by the selection of patients with liver-only disease, but also by the efficacy of radioembolization, which more than 70% of the study population received. The availability of radioembolization, together with its suggested activity and safety, could prevent the setting up of further randomized studies comparing radioembolization with best supportive care alone. Moreover current evolution of mCRC management toward complex, individually tailored, multidisciplinary approaches<sup>32</sup> could blur definitive analysis of each technique or therapy. These developments, along with the technical hurdles associated with intra-arterial locoregional access, will likely hamper more conclusive survival data to be collected on radioembolization in chemotherapy-refractory mCRC.

Assessment of response after radioembolization using standard morphology-based CT criteria (RECIST) reportedly lacks sensitivity (presence of necrosis, hemorrhage, and cystic changes rendering volumetry unreliable) and of specificity (edema, fibrosis, necrosis frequently undistinguishable from recurrent or residual tumor).<sup>33-35</sup> Several authors have reported the feasibility and superiority of metabolism-based imaging with FDG-PET.<sup>36-38</sup> However, the PET cameras at the three trial centers were not cross-calibrated, making a pooled analysis of the quantitative PET data unreliable. Nevertheless, we recently reported a subgroup analysis in eight patients treated with radioembolization at a single institution (Institut Bordet).<sup>21</sup> A significant metabolic response, expressed as a more than 50% reduction of the FDG uptake 6 weeks after radioembolization, was found in 19 (49%) of 39 lesions. This metabolic response rate was determined from the integration of data generated by multimodality structural (CT), functional (MAA-SPECT), and metabolic (FDG-PET) imaging. The central observation was that if a metabolically active metastasis on PET did not show an increased arterial vascularization on MAA-SPECT, the probability of responding to radioembolization was unacceptably low. Accepting the hypothesis that metabolic response is an accurate surrogate for disease control (TTLP), the implementation

**Table 4.** Incidence of Adverse Events

Event by CTC Grade	No. of Patients per Grade							
	FU Alone (n = 22)				Radioembolization + 5FU (n = 21)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
<b>Gastrointestinal</b>								
Stomatitis	1		1		1	1		
Diarrhea	1							
Nausea					4	1		
Vomiting	2				2			
Constipation	3							
Anorexia	4	2	1		4	1		
Gastrointestinal						1		
<b>Pain</b>								
Abdominal pain	2	1			3	1		
Myalgia	1				2			
Pain other	1							
<b>Constitutional</b>								
Fatigue	2	4	5		4	4		
Fever	1	2			2	1		
<b>Dermatology/skin</b>								
Skin		2						
Hand-foot syndrome		2					1	
<b>Pulmonary</b>								
Dyspnea		1	1					
Pulmonary			1					
<b>Neurology</b>								
Neurosensorial					2			
Cognitive disturbance		1				1		
Cardiac arrhythmia	1							
<b>Allergy/immunology</b>								
Allergy			1					
Other toxicity		1*			1†	1‡		

Abbreviations: CTC, Common Terminology Criteria for Adverse Events version 3.0; FU, fluorouracil.  
 \*Ascites.  
 †Thrombocytopenia.  
 ‡Stomach ulcer, ascites.

of such algorithms could allow better preselection of radioembolization candidates and improve cost-effectiveness and the per-patient benefit.

In this trial, and in contrast to a recently completed phase II study of radioembolization in patients with chemotherapy-refractory mCRC,<sup>27</sup> the tumor response by RECIST was disappointingly low. A partial response was achieved in only two patients (9.5%) compared with a response rate of 24% by RECIST with radioembolization alone in the study by Cosimelli et al.<sup>27</sup> The uncontrolled nature of the Cosimelli study and the known difficulty in assessing response using CT-based RECIST may account for this apparent discrepancy. The 10.0-month median overall survival with radioembolization plus FU in this current study is, however, comparable with the survival data from recent studies using <sup>90</sup>Y-resin microspheres in chemotherapy-refractory mCRC.<sup>26-28</sup>

Although these encouraging results suggest that radioembolization may offer a real clinical benefit to this population with dismal prognosis, questions remain regarding its use earlier in the disease course where the aim of radioembolization combined with systemic chemotherapy could consolidate the durability of response in the liver and increase the resectability of inoperable tumors.<sup>39</sup> Provisional evidence from a phase I trial combining <sup>90</sup>Y-resin microspheres with

infusional fluorouracil, leucovorin, and oxaliplatin in chemotherapy-naive patients were encouraging.<sup>23</sup> Results of randomized, multicenter, phase III trials are eagerly awaited.<sup>40</sup>

In conclusion, this randomized controlled trial met its primary end point by demonstrating that a single hepatic arterial injection of <sup>90</sup>Y-resin microspheres added to a standard PIV infusion of FU significantly extends the time to both local and overall disease progression. A better assessment of the radioembolization impact on survival in patients with chemotherapy-refractory disease requires randomized studies comparing it with best supportive care, the completion of which would be unrealistic given the current status of scientific knowledge. Treatment was well tolerated and did not add relevant toxicity. Radioembolization with <sup>90</sup>Y-resin microspheres should therefore be considered as a valid therapeutic option for patients with chemotherapy-refractory liver-limited mCRC.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked

with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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