Original Article

Hepatic imaging response to radioembolization with yttrium-90-labeled resin microspheres for tumor progression during systemic chemotherapy in patients with colorectal liver metastases

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Background: To assess response and the impact of imaging artifacts following radioembolization with yttrium-90-labeled resin microspheres (^{90}Y-RE) based on the findings from a central independent review of patients with liver-dominant metastatic colorectal cancer (mCRC).

Methods: Patients with mCRC who received ^{90}Y-RE (SIR-Spheres®; Sirtex Medical, Sydney, Australia) at nine US institutions between July 2002 and December 2011 were included in the analysis. Tumor response was assessed at baseline and 3 months using either the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 or 1.1. For each lesion, known artifacts affecting the interpretation of response (peri-tumoral edema and necrosis) were documented. Survivals (Kaplan-Meier analyses) were compared in responders [partial response (PR)] and non-responders [stable (SD) or progressive disease (PD)].

Results: Overall, 195 patients (mean age 62 years) received ^{90}Y-RE after a median of 2 (range, 1-6) lines of prior chemotherapy. Using RECIST 1.0 and RECIST 1.1, 7.6% and 6.9% of patients were partial responders, 47.3% and 48.1% had SD, and 55.0% and 55.0% PD, respectively. RECIST 1.0 and RECIST 1.1 showed excellent agreement {Kappa =0.915 [95% confidence interval (CI): 0.856-0.975]}. Peri-tumoral edema was documented in 32.8%, necrosis in 48.1% and both in 57.3% of cases (using RECIST 1.0). Although baseline characteristics were similar in responders and non-responders (P>0.05), responders survived significantly longer in an analysis according to RECIST 1.0: PR median (95% CI) 25.2 (range, 9.2-49.4) months *vs.* SD 15.8 (range, 9.3-21.1) months *vs.* PD 7.1 (range, 6.0-9.5) months (P<0.0001).

Conclusions: RECIST 1.0 and RECIST 1.1 imaging responses provide equivalent interpretations in the assessment of hepatic tumors following ^{90}Y-RE. Radiologic lesion responses at 3 months must be interpreted with caution due to the significant proportion of patients with peri-tumoral edema and necrosis, which may lead to an under-estimation of PR/SD. Nevertheless, 3-month radiologic responses were predictive of prolonged survival.

Keywords: Radioembolization (RE); colorectal cancer (CRC); 90Y-microsphere; hepatic imaging

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Background

The liver is a common site of metastasis among patients with colorectal cancer (mCRC) (1,2). Surgical resection, if possible, remains standard treatment for these tumors. However, several factors, including anatomical location of the tumor, extent of hepatic metastases, inadequate hepatic functional reserve, and comorbidities result in some 75-90% of patients being ineligible for surgical treatment (3). For these patients, local or regional therapy options are available.

Radioembolization (RE) with ytrium-90-labeled (^{90}Y) microspheres is a form of brachytherapy that exhibits anti-tumor activity via radiation damage from locally implanted microspheres (4). These microspheres are 30 microns in diameter, and are administered via hepatic vasculature so that they permanently implant in the terminal arterioles of hepatic tumors. Normal liver parenchyma adjacent to the tumor is spared injury because the mean penetration of beta radiation is 2.5 mm (and no greater than 11 mm) (4). In clinical studies, yttrium-90-labeled resin microspheres (^{90}Y-RE) has been combined with 5-fluorouracil, leucovorin, and oxaliplatin or irinotecan (i.e., FOLFOX or FOLFIRI) during first- or second-line chemotherapy, or administered alone or in combination with 5-fluorouracil in the refractory setting (5-8). Compared with systemic chemotherapy alone, clinical trials have demonstrated improvements in progression-free survival (PFS), overall survival (OS) and objective response rates with the addition of ^{90}Y-RE, even among heavily pre-treated patients (6-12). Despite the success of ^{90}Y-RE in prospective clinical trials, frequent questions still arise during tumor boards and patient consultations about the typical response to treatment and the reliability of Response Evaluation Criteria in Solid Tumors (RECIST) (13-15). Moreover, a recent review found that the time to response measured on CT varied widely between studies from 1.5 to 6 months (16); although the majority of studies, including a study by Kennedy *et al.* [2006] (17), found that the optimum time to response is at approximately 3 months post-procedure. The purpose of this retrospective study was to assess the imaging response at 3 months in patients with hepatic metastases secondary to colorectal cancer (CRC) who were treated with ^{90}Y-RE in community and academic cancer centers in the United States. Data from the primary analyses in the overall cohort are published elsewhere (18).

Methods

Selection of institutions and patient cases

Eleven of the 15 invited RE centers in the United States participated in a retrospective study of mCRC liver metastases outcomes after RE (MORE). Institutional review boards granted exemptions for each participating site prior to the start of data collection. Data were collected from source documentation by an independent contract research organization for all patients with a diagnosis of mCRC who were treated with ^{90}Y-resin microspheres (SIR-Spheres®; Sirtex Medical, Sydney, Australia) between July 2002 and December 2011 and had at least one follow-up visit. Patient identifiers were replaced with a unique study number. This imaging response report was conducted in a sub-cohort of patients from the MORE study of only those patients from nine centers with radiologic studies which meet our strict criteria of pre-treatment and post treatment time intervals. These were (I) within 30 days prior to ^{90}Y-RE, and (II) at 90 days (±30 days) post ^{90}Y-RE. Only these studies were analyzed via independent central imaging review and comprise the dataset for this report. A board-certified radiologist expert in post ^{90}Y-RE treated patients systematically reviewed abdominal computed tomography (CT) images (portal venous phase) collected at baseline and 3 months following the first ^{90}Y-RE procedure. Response to treatment was assessed using the RECIST versions 1.0 (19) and 1.1 (20), based on a maximum of five and two target lesions respectively (*Table 1*). Peri-tumoral edema and necrosis (known artifacts which can impact interpretation of response) were also documented for each lesion.

As per the published guidance at the time of the study (8,21-24), ^{90}Y-RE was considered for those patients with advanced liver-dominant mCRC who were not suitable for surgery, ablation or systemic therapy, and had progressed or become intolerant to at least one line of systemic therapy (*Table 2*). During the pre-treatment work-up, patients were excluded from RE if there was evidence of any uncorrectable flow to non-target sites (e.g., gastrointestinal tract or other extra-hepatic organs) observed on angiography or Technetium-99m macroaggregated albumin (^{99m}Tc-MAA) scans. Some patients, under exceptional circumstances and with informed consent, were treated outside the criteria outlined above based on the clinical judgment of the treating physicians. The protocol for treatment is reported elsewhere for the administration of ^{90}Y-resin microspheres

Table 1 Assessment of response by RECIST 1.0 and RECIST 1.1

Criteria	RECIST 1.0	RECIST 1.1	Comment
Minimum target lesion diameter by CT or MRI at baseline	≥20 mm	≥10 mm	Entry was restricted to those with measurable disease
Measurable lesions	Up to five per organ and ten lesions in total, representative of all involved organs	Up to two per organ and maximum of five lesions in total, representative of all involved organs	
Prior treatment	Tumor lesions that are situated in a previously irradiated area not considered measurable	Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion	
Non-target lesions	All other lesions (or sites of disease) were identified as non-target lesions and recorded at baseline	Multiple non-target lesions involving the same organ were assessed as a single item on the case record form (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases")	
Criteria for response (according to sum of target lesions diameters)			Confirmation of CR or PR after at least 28 days required for RECIST 1.0 only and for RECIST 1.1 if primary endpoint
CR	Disappearance of lesions	Disappearance of lesions	
PR	≥30% decrease	≥30% decrease	Both target and non-target lesions in the liver were assessed at follow-up
SD	<30% decrease or <20% increase	<30% decrease or <20% increase	
PD	Any increase	≥20% or ≥5 mm increase	Note: appearance of new lesion as indicator of progression is only relevant for overall response evaluation
PET	No specific recommendations	FDG-PET may be considered to complement CT scanning in assessment of progression and the confirmation of CR	Results from PET were not considered in this study

RECIST, Response Evaluation Criteria in Solid Tumors; CT, computed tomography; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PET, positron emission tomography.

within a single session or over multiple sessions (e.g., using a sequential lobar approach for bilobar liver metastases) (22). The body surface area methodology was mainly used in the activity calculations for ^{90}Y.

Statistical methodology

This study tested no formal hypotheses. Descriptive statistics were conducted using SAS version 9.2 XP Pro statistical analyses software (SAS Institute Inc., Cary NC, USA) to summarize patient characteristics. Estimates of OS were computed by response to treatment [partial response (PR) versus stable (SD) or progressive disease (PD)] and the activity delivered (with the first RE procedure and overall) using Kaplan-Meier product-limit method (25).

Table 2 Patient selection criteria upon initial investigation (prior to detailed work-up) for radioembolization (RE) with ^{90}Y-resin microspheres from 2002 onwards

Inclusion criteria
Patients ≥18 years
WHO/ECOG performance status of 0 to 2
Life expectancy of at least 3 months*
Liver-dominant metastases from colorectal cancer
Evidence of liver metastases, not treatable by surgical resection or local ablation with curative intent (determined at multidisciplinary team)
Progressed or become intolerant to at least one line of systemic therapy
With floxuridine (FUDR) during first-line therapy*
During first- or second-line chemotherapy on a clinical trial*
Serum bilirubin less than 2 mg/dL (34.2 μmol/L) (in the absence of a reversible cause*)
Serum albumin more than 30 g/L
Serum creatinine less than 17 mg/dL (150 μmol/L)
Adequate hematologic function (based on complete blood count with differential, platelet counts, prothrombin time and/or partial thromboplastin time)
Exclusion criteria
Evidence of ascites or cirrhosis
Portal hypertension (unless selective or superselective radioembolization can be performed*)
Previous radiotherapy to the upper abdomen (reviewed on a case-by-case basis*)
Excessive tumor burden with limited hepatic reserve*
Prior capecitabine chemotherapy (risk: benefits unknown)*

*, additional recommendations from Radioembolization Brachytherapy Oncology Consortium (REBOC) 2007.

Results

A total of 195 patients (male, 60%; Caucasian, 67%) received a median of 2 (range, 0-6) lines of chemotherapy prior to ^{90}Y-RE. Patient characteristics are summarized in *Table 3*. Median tumor/liver ratio at the start of ^{90}Y-RE was 15% [interquartile range (IQR): 24%]. Median ^{90}Y activity administered was 1.18 GBq (IQR: 0.59).

Response to treatment and OS

Best response and response at 3-month follow-up by RECIST 1.0 and 1.1 are shown in *Table 4*. Three-month responses were assessed in 131 patients, with a median time to follow-up of 82 days (IQR: 34). The median time to best response was 70 days (IQR: 55). This difference in median time to responses is due to the range of times accepted as the 3-month evaluation scan which included studies at 90±30 days. This was necessary as patients were not entered on a prospective trial and thus imaging studies were completed in a less strict time course which was intended to be 3 months after ^{90}Y-RE. There was good agreement between responses assessed by RECIST 1.0 and 1.1, for best response {kappa =0.96, [95% confidence interval (CI): 0.855-0.956]} and for the response at 3 months [kappa =0.915, (95% CI: 0.856-0.975)]. No significant differences in baseline characteristics for responders and non-responders were evident (P>0.05).

In patients for whom 3-month follow-up imaging was evaluated, necrosis and peri-tumoral edema (by RECIST 1.0) was documented in 48.1% and 32.8% of patients, respectively. Both necrosis and peri-tumoral edema were observed in 57.3% of patients. By RECIST 1.1, necrosis and peri-tumoral edema were observed in 41.2% and 29.8%, respectively, with both necrosis and peri-tumoral edema documented in 50.4% of patients.

Kaplan-Meier estimates of OS by response to treatment by RECIST 1.0 and RECIST 1.1 are shown in *Figures 1*,*2*, respectively. For both RECIST 1.0 and 1.1, response at 3 months significantly predicted survival (P<0.0001).

Table 3 Baseline characteristics (n=195)

Parameter	Results
Gender, n (%)	
Male	117 (60.0%)
Female	78 (40.0%)
Age, years	
Mean ± SD (range)	62±12.61 (range, 33.6-90.0)
>70 years	57 (29.2%)
Ethnicity, n (%)	
White or Caucasian	130 (86.1%)
Black or African American	14 (9.3%)
Other	3 (2.0%)
Asian	2 (1.3%)
Hispanic or Latino	2 (1.3%)
Unknown	44 (22.6%)
Primary tumor site, n (%)	
Colon:rectum	149 (76.4%):35 (17.9%)
Colorectal	11 (5.6%)
ECOG performance status, n (%)	
0	82 (42%)
1	36 (18.4%)
2	5 (2.5%)
Unknown	72 (36.9%)
Ascites, n (%)*	
None	187 (96.9%)
Controlled:uncontrolled	2 (1.0%):4 (2.1%)
Primary tumor *in situ*, n (%)	28 (14.4%)
Extra-hepatic metastases at radioembolization	
Any site, including: lung, lymph node(s), peritoneum, bone	67 (34.9%)
Prior treatment	
Liver-directed surgery and/or ablation	42 (21.5%)
Vascular/percutaneous procedure	8 (4.1%)
Radiotherapy procedure to upper abdomen	3 (1.5%)
Any prior procedure	46 (23.6%)
Prior chemotherapy lines	
Median (range)	2 (range, 0-6)
mCRC diagnosis to radioembolization, months	
Median (range)	13.7 (range,0.6-69.3)

*, there was data specific to ascites in only 193 of the 195 patients.

Relationship between activity delivered and response or OS

Further analyses found that there was no relationship between the total activity of ^{90}Y delivered and the response to RE, when assessed by either RECIST 1.0 (P=0.487) or RECIST 1.1 (P=0.710). However, patients who received a lower activity (<1 *vs.* ≥1 GBq) with the first RE procedure had a significantly prolonged survival: 15.7 (95% CI: 12.1-21.6) *vs.* 9.2 (95% CI: 8.1-11.2) months; P=0.006 (LogRank); as well as patients who received a lower activity (<1 *vs.* ≥1 GBq) overall: 17.4 (95% CI: 12.1-28.9) *vs.* 9.3 (95% CI: 8.2-12.1) months; P=0.011 (LogRank). However univariate assessment found no correlation across all activities delivered and OS (P=0.474).

Discussion

As a treatment for patients with hepatic metastases secondary to CRC, the addition of ^{90}Y-RE to systemic therapy has been shown to improve PFS, OS and response rate compared with chemotherapy alone in prospective clinical trials (6,9,10,12). This retrospective study sought to assess the imaging response in patients treated with ^{90}Y-RE in both community and academic cancer centers. Among the 195 patients included, disease control (PR or SD) was evident in 62.1% and 63.1% by RECIST 1.0 and 1.1, respectively, with a high rate of agreement between the two assessment methods. These results compare favorably with recent trials with newer therapies in mCRC (such as regorafenib), which achieved a disease control rate of 41.0% (PR: 1%; SD: 40%) in a similar cohort of chemorefractory patients (26). However, this study emphasizes the need for cautious interpretation of radiological response at 3 months with RE, with a significant proportion of patients' images demonstrating necrosis and/or peri-tumoral edema, which can lead to either underestimation of response or overestimation of progression. This reflects the findings of other research groups evaluating the early response with either ^{90}Y glass (27,28) or resin microspheres (29), especially when assessing the response to treatment at less than 3 months after the procedure (16).

As summarized in *Table 5*, contemporary studies reporting radiologic response after RE with either resin or glass ^{90}Y microspheres compare closely with the current study. When grouped by line of therapy—first-line (8-10,24) second or third-line (11,45) chemotherapy refractory disease (5,6,17,30-44) and mixed first-line

Table 4 Tumor responses by RECIST 1.0 and RECIST 1.1

Criteria	Best response (n=195)[#], n (%)	Response at 3 months (n=131)*, n (%)
Tumor response (RECIST 1.0)		
Partial response (PR)	20 (10.3)	10 (7.6)
Stable disease (SD)	101 (51.8)	62 (47.3)
Disease control rate (SD + PR)	121 (62.1)	72 (55.0)
Progressive disease (PD)	74 (37.9)	59 (45.0)
Tumor response (RECIST 1.1)		
Partial response (PR)	20 (10.3)	9 (6.9)
Stable disease (SD)	103 (52.8)	63 (48.1)
Disease control rate (SD + PR)	123 (63.1)	72 (55.0)
Progressive disease (PD)	72 (36.9)	59 (45.0)

[#], median time to best response: 70 days (IQR =55 days); *, median time to response assessment at 3 months: 82 days (IQR =34 days); RECIST, Response Evaluation Criteria in Solid Tumors.

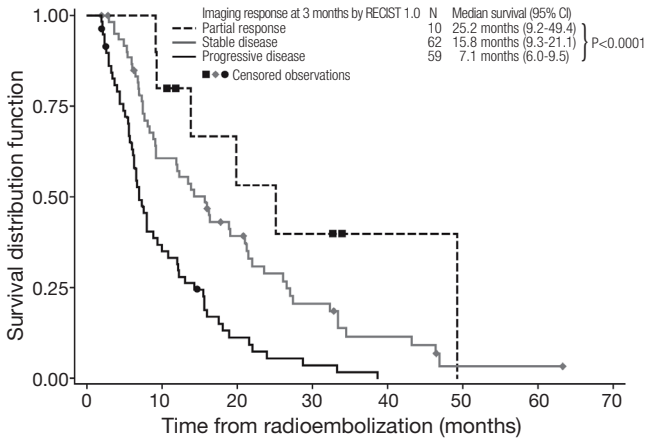

Figure 1 Overall survival (OS) by response at 3 months (by RECIST 1.0).

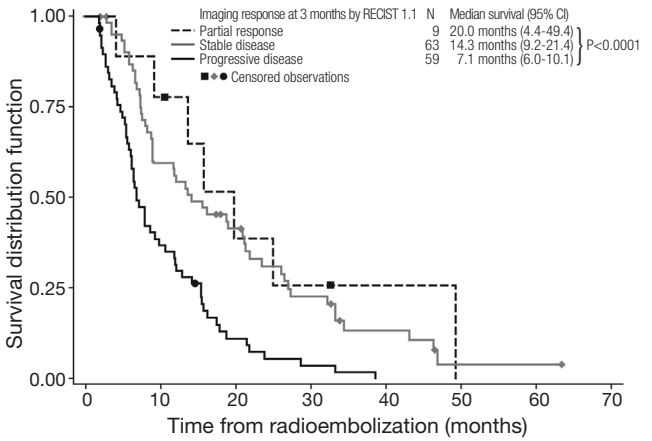

Figure 2 Overall survival (OS) by response at 3 months (by RECIST 1.1).

through chemotherapy refractory disease, there is a trend toward higher response earlier in the disease course.

Despite these caveats, radiological response to ^{90}Y-RE at 3 months appears to predict longer-term prognosis in the management of liver-dominant mCRC (5,43). We found that assessments of OS showed median survivals of 25.2 months for partial responders (by RECIST 1.0 at 3 months), with significantly shorter median survivals for patients with stable disease (15.8 months) or disease progression (7.1 months). These trends were similar when either RECIST 1.0 or RECIST 1.1 assessed responses at 3 months. Notably RECIST 1.1 requires the assessment of only two target lesions per organ (not less than 5 mm in size) instead of five as used in RECIST 1.0 (46); however, RECIST 1.1 has the advantage in that it may enable the more accurate diagnosis of progression (specified as an increase of 20% or more in the sum of the longest diameters of the target lesions), because it eliminates the interpretation of small increases in the tumor size as a significant increase in tumor burden (46). Although not assessed in this study, RECIST 1.1 also allows the findings from positron emission tomography (PET) to be considered in support CT findings, for PD and confirmation of complete response (CR) (16). Several studies assessing the prognostic value of response rate to ^{90}Y-RE have assessed CT findings in conjunction with tumor markers such as carcinoembryonic antigen (CEA) (38,43).

Beyond the measurement of anatomical changes in tumors, the development of functional imaging techniques

Table 5 Summary of published radiographic response rates following radioembolization (RE) in liver metastases from colorectal cancer

Study	Design	Microsphere type	Combination therapy *vs*. comparator	Liver-only or liver-dominant	Number evaluated for response	Response criteria	Response (%)					Median survival (months)
							CR	PR	SD	DCR	PD	
First-line												
Kosmider (10)	Retrospective	Resin	+ FOLFOX4 (63%)	LD	19	RECIST 1.0	11	74	5	89	11	29.4
			or 5FU/LV (37%)	LO subset	14		11	79	5	95	5	37.8
Sharma (8)	Prospective	Resin	+ FOLFOX	LD	20	RECIST 1.0	0	90	10	100	0	NA
van Hazel (9)	Prospective RCT	Resin	+ 5FU/LV	LD	11	RECIST 1.0	0	73	27	100	0	29.4
		–	*vs*. 5FU/LV	LD	10	RECIST 1.0	0	0	60	60	40	12.8
Gray (24)	Prospective RCT	Resin	+ FUDR-HAC	LO	32	WHO	6	44	41	91	9	39% at 2 y
		–	*vs*. FUDR-HAC	LO	27	WHO	0	22	48	70	30	29% at 2 y
Second-line or third-line												
Van Hazel (7)	Prospective	Resin	+ irinotecan	LD	23	RECIST 1.0	0	48	39	87	13	12.2
Lim (11)	Retrospective	Resin	+ 5FU in 70%	LD	32	RECIST 1.0	0	31	28	59	41	NA
Chemotherapy refractory disease												
Kalva (30)	Retrospective	Resin	None	LD	41	RECIST 1.1	0	2	83	85	15	6.1
Saxena (31)	Retrospective	Resin	None	LD	293	RECIST 1.0	1	38	33	72	29	10.5
Sofocleous (32)	Prospective	Resin	None	LD	19	RECIST 1.0	0	5	53	58	42	14.9
						PERCIST	0	33	20	53	47	
Benson (33)	Prospective	Glass	None	LD	58	RECIST 1.0-based	0	5	53	59	41	8.8
Smits (34)	Retrospective	Resin	None	LD	59	RECIST 1.1^{TL}	3	5	27	35	27	8.9
Seidensticker (35)	Prospective	Resin	+ BSC	LD	28	RECIST 1.0	0	43	18	62	38	8.3
	Retrospective	–	*vs*. BSC (matched-pairs)	LD	NA (of 29)	NA	NA	NA	NA	NA	NA	3.5
Martin (36)	Retrospective	Not defined	None	LD	24	RECIST 1.1	0	0	NA	NA	NA	8.9
Zerizer (37)	Retrospective	Resin	+ FOLFOX in 20%	LD	25	RECIST 1.1^{TL}	0	8	92	100	0	NA
						EORTC PET	0	60	40	60	0	
						Choi	0	8	84	92	8	
Nace (38)	Retrospective	Resin	+ FUDR HAC in 33%	LD	31	RECIST 1.0	0	13	65	77	23	10.2
Cosimelli (5)	Prospective	Resin	None	LD	46	RECIST 1.0	2	24	26	52	48	12.6
Hendlisz (6)	Prospective RCT	Resin	+ 5FU	LO	20	RECIST 1.0	0	10	80	90	10	10.0
		–	*vs*. 5FU (> SIRT at PD)	LO	22	RECIST 1.0	0	0	36	36	64	7.3
Cianni (39)	Retrospective	Resin	None	LD	41	RECIST 1.0	5	40	36	81	19	11.9
Jakobs (40)	Retrospective	Resin	None	LD	36	RECIST 1.0	0	19	70	89	11	10.5
Kennedy (17)	Retrospective	Resin	None	LD	208	WHO	0	36	55	91	10	10.5^{R}; 4.5^{NON-R}
Mixed setting (first-line through chemotherapy refractory disease)												
Chua (41)	Retrospective	Resin	None	LD	140	RECIST 1.0	1	31	31	63	37	9.0
Mulcahy (42)	Prospective	Glass	None	LD	72	WHO	0	40	45	85	15	14.5
Stubbs (43)	Retrospective	Resin	+ HAC with 5FU	LD	80	Author-defined	1	73	20	94	6	11.0
Lewandowski (44)	Prospective	Glass	None	LD	26	WHO	0	35	52	87	13	9.3

LO, liver-only metastases; LD, liver-dominant metastases; CR, complete response; PR, partial response; SD, stable disease; DCR, disease control rate (CR + PR + SD); PD, progressive disease; RCT, randomized controlled trial; FUDR-HAC, floxuridine-hepatic arterial chemotherapy; NA, not available; BSC, best supportive care; TL, response in target lesions; R, (survival in) responders; NON-R, (survival in) non-responders; y, years; RECIST, Response Evaluation Criteria in Solid Tumors.

including diffusion-weighted magnetic resonance imaging (DW-MRI) for hepatocellular carcinoma (HCC) (47-49) and mCRC (50-52), gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging (Gd-EOB-DTPA) in HCC and mCRC (52,53), and PET for liver metastases (14,27,29,44,54,55) have allowed for the earlier (between 6-8 weeks post-procedure) and/or more sensitive assessment of treatment response compared with CT using RECIST (29,56). More recently, changes in metabolic volume and total lesion glycolytic rate as measured by fluorine-18 fluorodeoxyglucose (^{18}F-FDG) PET in response to ^{90}Y-RE has shown to be predictive of survival (57) while changes in maximum standardized uptake value (SUV_{max}) on ^{18}F-FDG PET have shown to be predictive of PFS (37). As imaging techniques evolve, the utility of pretreatment imaging (such as contrast-enhanced CT perfusion of liver metastases) in predicting potential responders and survival following ^{90}Y-RE prior presents an intriguing new development (58); although further validation of these imaging techniques is still needed before they are adopted in clinical practice. Currently, several multicenter phase III trials with ^{90}Y-RE are ongoing including SORAMIC which is evaluating Gd-EOB-DTPA-MRI in HCC, while the SIRFLOX and the FOXFIRE studies in mCRC are evaluating the response using RECIST 1.0 and modified RECIST, respectively.

The study also found that patients who received a low activity (<1 GBq of ^{90}Y), probably reflecting a lower disease burden in the liver, had a significantly longer survival than patients who were required higher activities of ^{90}Y. Overall, the activity delivered was not predictive of response at 3 months when measured by RECIST 1.0 or RECIST 1.1 in this cohort of patients.

The main limitation of this study is the retrospective nature of analyses. The MORE study permitted a broader range of patients than would otherwise be included within conventional clinical trials with chemotherapy (from some who received ^{90}Y-RE as a first-line therapy to others who received ^{90}Y-RE in the chemorefractory setting after three or more prior lines of chemotherapy). Nevertheless, careful guidance in the selection of patients based on published consensus from the RE Brachytherapy Oncology Consortium (REBOC) and other earlier reviews (21-23) allowed for the inclusion of patients of a similar stage (with liver-dominant disease and an ECOG performance status 0-1). This homogeneity was important to our findings since baseline factors such as extrahepatic disease as well as ECOG performance status are also important predictors of survival following ^{90}Y-RE (10,38).

In conclusion, while this study is not without the limitations common to all retrospective studies, it provides a unique assessment of tumor response after ^{90}Y-RE in patients treated in both community and academic cancer centers. Even in these unselected patients, the benefit of ^{90}Y-RE for patients with unresectable hepatic metastases secondary to CRC is evident.

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Footnote

Conflicts of Interest: DM Coldwell is a consultant to Sirtex Medical; M Cohn, A Drooz, FM Moeslein, CW Nutting, SG Putnam 3rd, SC Rose, EA Wang are proctors for Sirtex Medical; MA Savin is a speaker for BSD Medical.
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Prior presentations: AS Kennedy *et al*. GI ASCO 2013.

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