Original Article

Updated survival outcomes and analysis of long-term survivors from the MORE study on safety and efficacy of radioembolization in patients with unresectable colorectal cancer liver metastases

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Background: The Metastatic colorectal cancer liver metastases Outcomes after RadioEmbolization (MORE) study was a retrospective analysis of 606 patients with unresectable colorectal liver metastases treated with radioembolization (RE) using ^{90}Y-labeled resin microspheres. The first analysis of this study was completed with a last patient follow-up of 77.7 months. We now provide an updated survival analysis through September 15, 2016, with a last patient follow-up of 125 months.

Methods: ^{90}Y-RE was considered for patients with advanced liver-only or liver-dominant metastatic colorectal cancer which was deemed not suitable for surgery, ablation, or systemic therapy, and which had progressed or become refractory to at least one line of systemic therapy. All patients with a diagnosis of metastatic colorectal cancer who had received at least 1 RE treatment and 1 follow-up visit were included in the analysis. Patients were treated between July 2002 and December 2011 at one of 11 U.S. tertiary care centers. Data were collected at baseline, on the day of the first ^{90}Y-RE treatment (day 0), and at all subsequent visits or until death. Patient medical charts and/or public records were accessed to obtain dates of death.

Results: Dates of death were obtained for 574 out of a total of 606 patients, and overall survival (OS) data analyzed. Updated median OS was 10.0 months (95% CI: 9.2-11.8 months) at a median follow-up of 9.5 months versus the originally reported median OS of 9.6 months (95% CI: 9.0-11.1 months) at a follow-up of 8.6 months in the first MORE analysis. Patients received a median (range) of 2 (0 to 6) lines of chemotherapy. Baseline characteristics and factors significantly associated with patient survival ($P<0.01$) are consistent with those reported in the first safety analysis of the MORE study. These factors include poor ECOG performance status, markers of advanced disease such as increased extent of tumor-to-target liver involvement, poor baseline liver function, pre-treatment anemia, lung shunt fraction, and number of lines of prior chemotherapy. Patient age did not significantly affect survival outcomes.

Conclusions: Long-term follow-up confirms that ^{90}Y-RE treatment offers favorable survival benefits for patients with unresectable metastatic colorectal cancer, even among patients who received 3 or more prior lines of chemotherapy. Our analysis also supports earlier reported prognostic factors for survival after ^{90}Y-RE. Overall, our updated analysis confirms that ^{90}Y-RE treatment provided a meaningful response and survival advantage for MORE patients across all ages and across diverse community and academic centers in the U.S.

Keywords: Colorectal neoplasms; brachytherapy; yttrium radioisotopes; salvage therapy

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Introduction

Colorectal cancer is the third most commonly diagnosed cancer in the United States (U.S.) for both men and women, and the second most common cause of cancer-related mortality. It is estimated that in 2016, 134,490 new cases of colorectal cancers will be diagnosed in the U.S. and 49,190 people will die from this disease (1). The 5-year survival rate for patients diagnosed with localized disease is 90%; however, the 5-year survival rate for patients diagnosed with metastatic disease is only 13% (1). The most common site of metastasis is the liver (2). More than half of patients diagnosed with colorectal cancer present with or eventually develop liver metastases, only 10%–20% of which are resectable at presentation. A percentage of these metastases may be downstaged for surgery by treatment with chemotherapy and targeted agents (2,3). However, patients with liver metastases which remain unresectable have a poor prognosis and are generally given second-line chemotherapy, with a median survival of approximately one year (3).

For patients with unresectable colorectal cancer liver metastases that are refractory to first-line chemotherapy, a variety of interventional radiological procedures may also be considered (4-6). One such treatment is radioembolization (RE), also known as selective internal radiation therapy (SIRT), with yttrium-90-labeled (^{90}Y) microspheres. This treatment modality consists of the selective delivery of radioactively labeled particles to liver tumors via the hepatic artery. Selective delivery of ^{90}Y microspheres to tumors can be achieved because hepatic tumors receive most of their blood supply from the hepatic artery, while normal hepatic tissue receives blood mainly from the portal vein (4,7).

In 2015 first results from the Metastatic colorectal cancer liver metastases Outcomes after RadioEmbolization (MORE) study, a retrospective analysis of 606 patients with unresectable colorectal liver metastases treated with RE using ^{90}Y-labeled resin microspheres (SIR-Spheres®) were published. Patients were treated between July 2002 and December 2011 at one of 11 tertiary care centers in the U.S., and received a median of 2 (range, 0-6) lines of chemotherapy prior to treatment with RE. At a median follow-up of 8.6 months, median survivals of patients following RE as a 2nd-line, 3rd-line, or 4th-plus line therapy were 13.0 (range, 10.5–14.6), 9.0 (range, 7.8–11.0), and 8.1 (range, 6.4–9.3) months, respectively (8). These survival times compare favorably to those of patients treated with chemotherapy and other systemic therapies in similar settings (8-11). This initial analysis concluded that ^{90}Y-RE appeared to have a favorable survival benefit for these patients. Importantly, it noted an apparent favorable survival benefit even for patients who had received ≥3 lines of prior chemotherapy (^{90}Y-RE as a 4th-plus line treatment) (8). Subsequent analyses from the MORE study have examined the safety and efficacy of ^{90}Y-RE within the subgroup of elderly patients ≥70 years, and have examined baseline patient characteristics associated with long-term survival. A summary of key points from previous publications from the MORE study is given in *Box 1*.

This paper reports updated survival outcomes from the MORE study through September 15, 2016, reflecting an additional 138 person-years of follow-up from the first published analysis. A sub-cohort of long-term survivors who were still alive a year or more after first RE treatment are identified, and sub-analysis of these long-term survivors with a focus on baseline patient characteristics and treatment-related factors associated with long-term survival is reported as well. Our overall analysis contributes to a developing body of literature from the original MORE study, which continues to be one of the largest studies to date of metastatic colorectal cancer patients who received ^{90}Y-RE alone after failed lines of chemotherapy.

Methods

Study design, patient selection, and treatment

The MORE study (clinicaltrials.gov identifier: NCT01815879) was an investigator-initiated retrospective study of 606 patients with colorectal cancer liver metastases who were consecutively treated with RE using ^{90}Y resin microspheres (SIR-Spheres®). Patients were treated between July 2002 and December 2011 at one of 11 U.S. tertiary care centers, and data at each site were collected from source documentation by an independent contract research organization. Each site was granted institutional review board exemptions prior to data collection. All patients with a diagnosis of metastatic colorectal cancer who had received at least 1 RE treatment and 1 follow-up visit were included in the analysis.

Centers were guided in the selection of patients, pre-treatment work-up, and RE by the published consensus from the Radioembolization Brachytherapy Oncology Consortium (REBOC) and earlier reviews (15-17). In summary, ^{90}Y-RE was considered for advanced liver-only or liver-dominant metastatic colorectal cancer, which was deemed not suitable for surgery, ablation, or systemic therapy, and which had progressed or become refractory to at least one line of systemic therapy. Candidates for ^{90}Y-RE had Eastern Cooperative Oncology Group (ECOG) performance status score of up to 2 and untreated life expectancy of at least 12 weeks. Patients with signs of liver failure or compromised bone marrow or pulmonary function were considered unsuitable for ^{90}Y-RE. However, under exceptional

Box 1 Key prior findings from the Metastatic colorectal cancer liver metastases Outcomes after RadioEmbolization (MORE) Study

Background of the MORE study: Retrospective analysis of 606 patients with unresectable colorectal liver metastases treated with ^{90}Y-RE. Patients had received a median of 2 (range, 0–6) lines of prior chemotherapy (8).

Initial analysis: (median follow-up of 8.6 months). ^{90}Y-RE was well tolerated and appeared to offer a favorable survival benefit for patients, with median survival times similar to those of patients treated with chemotherapy alone in similar settings (8).

Key findings from subsequent analyses:

- A subgroup analysis of patients >70 years *vs.* patients <70 years found that overall survival and toxicities did not differ between these age groups, indicating that ^{90}Y-RE appears well-tolerated and effective even in the very elderly (12).
- Low baseline hemoglobin levels and laboratory values indicative of liver dysfunction (levels of albumin, alkaline phosphatase, aspartate aminotransferase, alanine transaminase, bilirubin, and creatine) were significantly associated with decreased median survival times across all lines of prior chemotherapy (13).
- Liver shunt fraction (LSF) >10% was predictive of significantly decreased patient survival time compared to LSF <10% (median survival, 6.9 months *vs.* 10.0 months; hazard ratio, 1.60; P<0.001) (14).

circumstances and with informed consent, some patients were treated outside the outlined criteria based on the clinical judgement of individual treating physicians.

Data collection and analysis

Patient medical charts and/or public records were accessed to obtain date of death (DOD). Adverse events (AEs), baseline patient tumor characteristics, and treatment histories were previously collected as described (8,14). Briefly, data were collected at baseline, on the day of the first ^{90}Y-RE treatment (day 0), and at all subsequent visits or until death. All results from liver function, hematologic, and blood biochemistry tests were recorded and submitted to a centralized data collection center. The National Cancer Institute Common Toxicity Criteria Adverse Events version 3.0 was used as a tool to grade both the nature and severity of all AEs (18). Survival was calculated with the first day of ^{90}Y-RE treatment serving as day 0 to the day of death or last follow-up.

Statistical analysis

Overall and stratified survival were estimated by the Kaplan-Meier method, and the log-rank test used to assess statistical significance. Median survival (months) and the 95% confidence interval were reported. Comparisons of prognostic variables and survival at 1 year (yes, no) include ANOVA for continuous variables, Fisher's exact test for dichotomous variables, Chi-square general association for categorical variables, and Wilcoxon rank sum test for ordinal variables. P-values for this analysis exclude patients who did not survive 1 year and were censored, and consistency of survival comparisons in all patients was confirmed.

P-values were calculated as follows: for continuous variables, ANOVA; for dichotomous variables, Fisher's exact test; for nominal categorical variables, Chi-Square general association test; for ordinal variables, Wilcoxon rank sum test.

Results

Updated survival analysis of the entire MORE cohort

In this paper, we report extended survival surveillance of the remaining MORE patients through September 15, 2016, at a median follow-up of 9.5 months. During this analysis, death dates were obtained for an additional 71 patients. In all, death dates were confirmed for 574 patients out of 606, or 95% of all enrolled patients. Updated Kaplan-Meier estimates of OS were reported at half-year intervals through 5 years (*Table 1*). The survival percentage at 1, 2, and 3 years following ^{90}Y-RE was 45%, 18.9%, and 7.0%, respectively. The updated overall median survival was 10.0 months (95% CI: 9.2–11.8 months) at a median follow-up of 9.5 months versus the originally reported 9.6 months (95% CI: 9.0–11.1 months) at a median follow-up of 8.6 months as reported in the first MORE study analysis (8).

An updated survival analysis of patients stratified by baseline patient characteristics and treatment factors was also performed (*Figures 1,2* and *Table 2*). Factors significantly associated with patient survival (P<0.01) are consistent with those reported in the first published safety analysis of the MORE study (8). These factors include poor ECOG performance status, markers of advanced disease (extra-hepatic metastases, elevated levels of carcinoembryonic antigen [CEA], increased extent of tumor-to-target liver involvement), and increased lines of chemotherapy. Poor liver function at baseline is also significantly associated with poor survival, as demonstrated by presence of ascites and the results of liver enzyme tests. Specifically, we found that abnormal levels of

Table 1 Kaplan-Meier estimates of overall survival time at half-year intervals through 5 years

Follow-up month, 0 to interval	Percentage, survival	Percentage death	Standard Error	Cumulative, number dead	Number remaining	Number censored
0	100.0	0.0	0.00	0	606	0
6	71.7	28.3	1.85	169	425	12
12	45.0	55.0	2.05	326	263	5
18	27.1	72.9	1.84	429	153	7
24	18.9	81.1	1.64	475	105	2
30	11.7	88.3	1.35	515	65	0
36	7.0	93.0	1.08	541	39	0
42	4.7	95.3	0.893	554	26	0
48	2.9	97.1	0.708	564	16	0
54	2.3	97.7	0.640	567	13	0
60	2.1	97.9	0.616	568	11	5
125 (last follow-up)				574	0	0

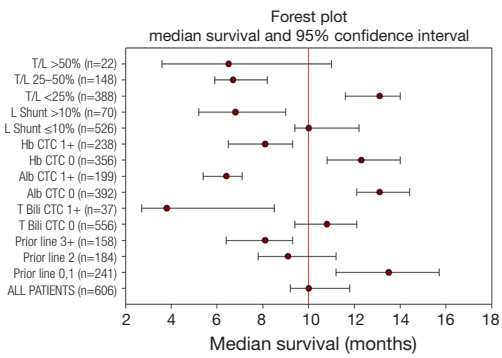

Figure 1 Forest plot of key factors associated with overall survival in patients with metastatic colorectal cancer liver metastases. For each subgroup, the median survival and 95% lower and upper confidence intervals are presented. Vertical line represents the median survival for all patients.

albumin, alkaline phosphatase, aspartate aminotransferase, and bilirubin at baseline are all associated with poor survival. Lung shunt fraction >10% and pre-treatment anemia (hemoglobin CTC grade ≥1) were also significantly associated with poor survival (*Table 2* and *Figures 1,2*).

Subgroup analysis of long-term survivors

As of September 2016, 263 of 606 total patients were confirmed to have survived for at least 1 year following first ^{90}Y-RE treatment. Subgroup analysis was performed of this set of long-term survivors with the goal of identifying predictors of long-term survival. As anticipated, baseline characteristics and treatment-related factors significantly associated with survival 1 year (P<0.01) overlapped with factors generally associated with survival outcomes (*Table 2* and *Table 3*), including indicators of advanced disease, liver function, hemoglobin levels (anemia), and number of lines of prior chemotherapy.

Discussion

The MORE study is the largest to date of metastatic colorectal cancer patients who received ^{90}Y-RE as monotherapy after failed lines of systemic therapy. Initial analysis of this study examined safety and efficacy of ^{90}Y-RE in this patient population. Subsequent analyses focused more closely upon baseline characteristics and factors associated with OS in these patients. Here we present an updated survival analysis from long-term follow-up of the MORE patients. Extending through September 2016, our analysis was initiated more than 14 years ago, and includes dates of death for 574 out of 606 patients, or 95% of our starting patient population.

Our results confirm that ^{90}Y-RE treatment appears to offer survival benefits for patients with unresectable colorectal cancer liver metastases refractory to first-line chemotherapy. Patients treated with ^{90}Y-RE in the second-line setting (after 1 line of failed chemotherapy) had a median survival

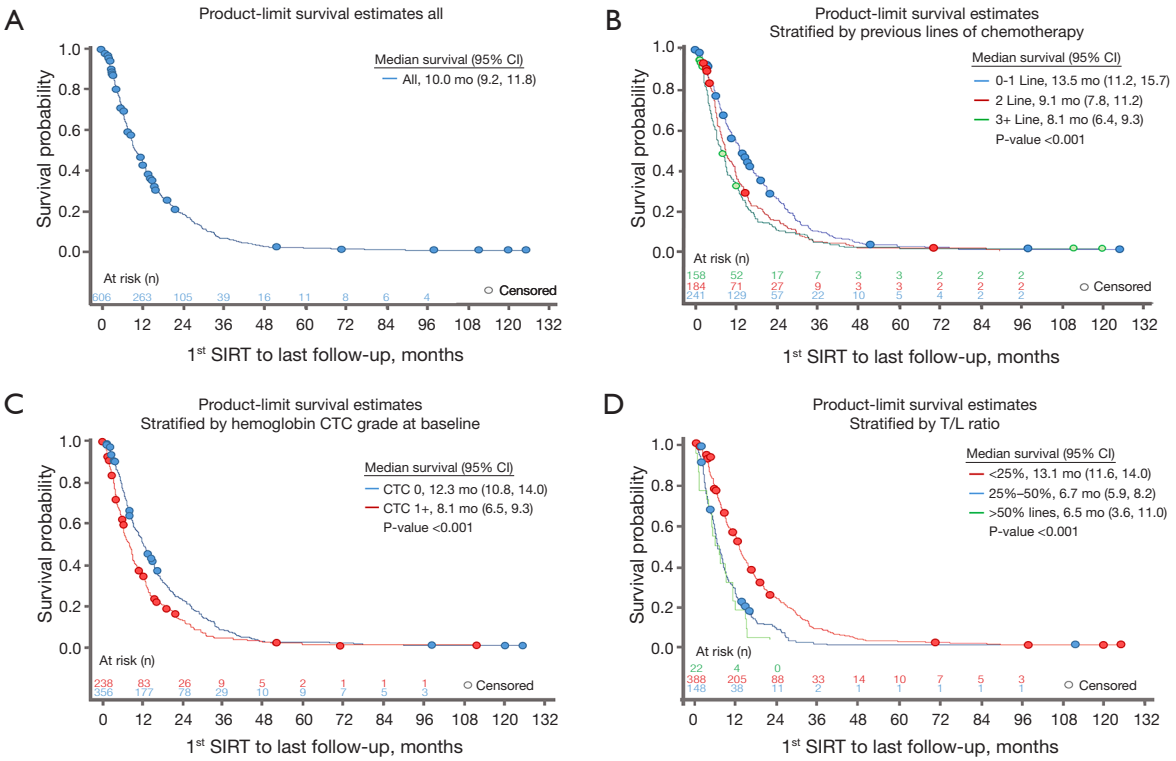

Figure 2 Kaplan-Meier curves of overall patient survival and patient survival stratified by key factors. Censored observations are represented by circles. Number of patients at risk are provided at yearly intervals. (A) Survival estimates for all patients; (B) Survival estimates stratified by previous lines of chemotherapy; (C) Survival estimates stratified by hemoglobin CTC grade at baseline; (D) Survival estimates stratified by tumor/target-liver ratios.

time after ^{90}Y-RE of 13.2 months (*Table 2*). This is similar to that of comparable patients treated in the second-line setting with the irinotecan-based FOLFIRI regimen alone (12.06 months) or combined with the antiangiogenic agent aflibercept (13.50 months) (9). It also compares favorably with survival times of metastatic colorectal cancer patients treated with second-line oxaliplatin or irinotecan-based chemotherapy alone (9.8 months median survival) or in combination with bevacizumab (median survival 11.2 months) (10). MORE patients treated with ^{90}Y-RE as third-line treatment (i.e. after 2 failed lines of chemotherapy) had a median survival of 9.1 months, and patients treated with ^{90}Y-RE as fourth-line therapy or higher (i.e. after 3 failed lines of chemotherapy or more) had a median survival time of 8.1 months (*Table 2*). These survival times compare favorably with similar patients treated with systemic therapies in the third-line setting or higher. For instance, metastatic colorectal cancer patients in the CONCUR trial were treated with the multikinase inhibitor regorafenib after at least 2 prior lines of failed therapy; these patients had a median survival of 8.8 months on regorafenib (6.3 months on placebo group) (19). Metastatic colorectal cancer patients treated with TAS-102, an oral agent combining trifluridine and tipiracil hydrochloride, after at least 2 prior lines of failed therapy had a median survival time of 7.1 months (5.3 months on placebo) (20). Overall, our results indicate that ^{90}Y-RE treatment for metastatic colorectal cancer patients in the second-line setting or higher may offer survival benefits for appropriate patients (i.e. those with unresectable liver-dominant or liver-only disease).

Our results show that the number of prior lines of chemotherapy is a significant predictor of survival following ^{90}Y-RE in our patient population. This confirms results from the first analysis of the MORE study (8). Our updated analysis also identified other factors significantly associated with survival, again consistent with previous analyses of the MORE data. These factors include high tumor burden in the liver, laboratory values indicative of poor liver function at baseline (e.g. total bilirubin and albumin levels), low levels of hemoglobin indicative of pre-treatment anemia, and lung shunt fraction greater than 10% (*Table 2*). Screening of such

Table 2 Updated survival analysis of all patients in the MORE study, stratified by baseline characteristics*

Characteristic	N	Survival, months		P-values between subgroups, P-value (log-rank)
		Median	95% CI	
All	606	10.0	9.2–11.8	
Sex				0.59
Female	233	9.5	8.9–12.1	
Male	373	10.4	9.1–12.2	
Age				0.26
<70 years	446	10.4	9.2–12.0	
≥70 years	160	9.4	8.0–12.1	
ECOG performance status				0.004
0	168	11.2	9.2–13.1	
1	72	8.5	6.5–12.8	
2	14	5.5	2.3–12.2	
3	3	5.0	1.3–11.0	
Ascites				<0.001
No	563	10.8	9.3–12.1	
Yes (controlled)	5	2.4	0.7–22.9	
Yes (uncontrolled)	23	5.5	3.8–7.4	
Extra-hepatic metastases				<0.001
No	393	12.3	11.2–13.9	
Yes	213	7.7	6.4–8.7	
In-situ primary				0.01
No	522	10.5	9.2–12.1	
Yes	78	8.2	6.3–12.0	
Metastases				0.015
Metachronous	173	11.3	9.2–13.9	
Synchronous	396	9.4	8.7–11.1	
Tumor-to-target liver involvement				<0.001
<25%	388	13.1	11.6–14.0	
25-50%	148	6.7	5.9–8.2	
>50%	22	6.5	3.6–11.0	
Prior lines of chemotherapy				<0.001
0 (RE 1st line)	35	15.6	9.3–21.4	
1 (RE 2nd-line)	206	13.2	10.9–15.5	
2 (RE 3rd-line)	184	9.1	7.8–11.2	
3+ (RE 4^{th+} line)	158	8.1	6.4–9.3	

Table 2 (*continued*)

Table 2 (*continued*)

Characteristic	N	Survival, months		P-values between subgroups, P-value (log-rank)
		Median	95% CI	
Lung shunt				<0.001
≤10%	526	10.8	9.4–12.2	
>10%	70	6.8	5.2–9.0	
Albumin, CTC grade				<0.001
0	392	13.1	12.1–14.4	
≥1	199	6.4	5.4–7.1	
Alkaline phosphatase, CTC grade				<0.001
0	241	16.3	14.4–18.3	
≥1	351	7.2	6.5–8.2	
Aspartate aminotransferase, CTC grade				<0.001
0	296	14.6	13.0–15.9	
≥1	294	7.4	6.4–8.7	
Carcinoembryonic antigen				<0.001
<median (62.2)	215	15.6	13.1–17.7	
≥median (62.2)	215	7.4	6.6–8.5	
Hemoglobin, CTC grade				<0.001
0	356	12.3	10.8–14.0	
≥1	238	8.1	6.5–9.3	
Total bilirubin, CTC grade				0.013
0	556	10.8	9.4–12.1	
≥1	37	3.8	2.7–8.5	

*, P-value by ANOVA for continuous variables, etc., as described in Methods.

baseline factors may be used to optimize patient selection for ^{90}Y-RE treatment. It has also been previously suggested that correction of anemia before ^{90}Y-RE treatment (for instance, by blood transfusion or subcutaneous erythropoietic) may improve survival outcomes (13). Consistent with a previous report, we found no significant difference in survival outcomes between elderly patients ≥70 years and those younger (*Table 2*). This confirms our earlier conclusion that ^{90}Y-RE is a safe and effective treatment for elderly patients with unresectable colorectal cancer liver metastases, and that age should not be a criteria for exclusion from this treatment (12).

^{90}Y-RE has traditionally been administered as treatment for metastatic colorectal cancer liver metastases after failure of chemotherapies and other systemic therapies to control the disease (4-6). In 2017, based partly upon earlier analyses of the MORE study as well as other supporting studies, the National Comprehensive Cancer Network (NCCN) adopted new guidelines recommending ^{90}Y-RE as a treatment option (category 2A evidence) for highly selected patients suffering from chemotherapy-resistant or chemotherapy-refractory metastatic colorectal cancer with predominant liver metastases (2017 NCCN guidelines in preparation). As of this moment, the great majority of metastatic colorectal cancer patients treated with ^{90}Y-RE receive it as salvage therapy (i.e. after first receiving 2 or more failed lines of chemotherapy) (7). The patient population of the MORE study reflects this general practice; patients received a median of 2 (range, 0-6) lines of chemotherapy prior to ^{90}Y-RE. Current research, however, has begun to focus upon the use of ^{90}Y-RE in combination with chemotherapy as first-line treatment for colorectal

Table 3 Baseline characteristics stratified by patients who survived (or were lost to follow-up) for at least 1 year *vs.* those who did not

Characteristic	Total, (N=606)	Survived at least 1 year (or more), >1 year , (N=263)	Survived less than 1 year, <1 year, (N=343)	P-value
Gender				0.932
Female	233 (38.4)	100 (38.0)	133 (38.8)	
Male	373 (61.6)	163 (62.0)	210 (61.2)	
ECOG				0.117
0	168 (65.4)	77 (70.0)	91 (61.9)	
1	72 (28.0)	29 (26.4)	43 (29.3)	
2	14 (5.4)	4 (3.6)	10 (6.8)	
3	3 (1.2)	0	3 (2.0)	
Ascites				0.005
No	563 (95.3)	252 (98.1)	311 (93.1)	
Yes (controlled)	5 (0.8)	2 (0.8)	3 (0.9)	
Yes (uncontrolled)	23 (3.9)	3 (1.2)	20 (6.0)	
Extrahepatic metastases				<0.001
No	393 (64.9)	199 (75.7)	194 (56.6)	
Yes	213 (35.1)	64 (24.3)	149 (43.4)	
Tumor/target liver involvement				<0.001
<25%	388 (69.5)	205 (83.0)	183 (58.8)	
25%–50%	148 (26.5)	38 (15.4)	110 (35.4)	
>50%	22 (3.9)	4 (1.6)	18 (5.8)	
Prior chemotherapy lines				<0.001
0 (RE 1st line)	35 (6.0)	20 (7.9)	15 (4.5)	
1 (RE 2nd line)	206 (35.3)	109 (43.3)	97 (29.3)	
2 (RE 3rd line)	184 (31.6)	71 (28.2)	113 (34.1)	
3+ (RE 4^{th+} line)	158 (27.1)	52 (20.6)	106 (32.0)	
Lung shunt				0.014
≤10%	526 (88.3)	238 (91.9)	288 (85.5)	
>10%	70 (11.7)	21 (8.1)	49 (14.5)	
Albumin, CTC grade				<0.001
0	392 (66.3)	208 (80.3)	184 (55.4)	
1+	199 (33.7)	51 (19.7)	148 (44.6)	
Alkaline phosphatase, CTC grade				<0.001
0	241 (40.7)	154 (59.7)	87 (26.0)	
1+	351 (59.3)	104 (40.3)	247 (74.0)	
Aspartate amino-transferase, CTC grade				<0.001
0	296 (50.2)	170 (65.9)	126 (38.0)	
1+	294 (49.8)	88 (34.1)	206 (62.0)	<0.001

Table 3 (*continued*)

Table 3 (*continued*)

Characteristic	Total, (N=606)	Survived at least 1 year (or more), >1 year , (N=263)	Survived less than 1 year, <1 year, (N=343)	P-value
Carcinoembryonic antigen (CEA), median (IQR) (ng/mL)	430 patients, 62.2 (283.4)	193 patients, 26.6 (146.3)	237 patients, 121.4 (430.3)	
Hemoglobin, CTC grade				<0.001
0	356 (59.9)	177 (68.1)	179 (53.6)	
1+	238 (40.1)	83 (31.9)	155 (46.4)	
Bilirubin, CTC grade				0.015
0	556 (93.8)	249 (96.5)	307 (91.6)	
1+	37 (6.2)	9 (3.5)	28 (8.4)	

*, P-value by ANOVA for continuous variables, etc., as described in methods. P-value excludes patients who did not survive 1 year and were censored.

cancer liver metastases. An early phase II trial demonstrated that addition of ^{90}Y-RE to fluorouracil and leucovorin-based chemotherapy in patients with colorectal cancer liver metastases improved time to progressive disease as well as overall median survival (29.4 median months for patients treated with chemotherapy plus ^{90}Y-RE versus 12.8 months for patients treated with chemotherapy alone, P=0.02) (21). In 2007, results from a phase I study demonstrated that ^{90}Y-RE could be safely combined with oxaliplatin-based chemotherapy (22). Based upon such small-scale studies, 3 large-scale phase III trials have been initiated to examine the effect of ^{90}Y-RE addition to oxaliplatin-based chemotherapy in treatment of metastatic colorectal cancer liver metastases in the first-line setting. A pooled analysis of survival outcomes from these 3 trials, the SIRFLOX, FOXFIRE, and FOXFIRE-Global clinical trials, will cover data from over 1000 patients. Survival outcomes are expected to be announced in 2017 (23). Data already available from the SIRFLOX trial has demonstrated that the addition of ^{90}Y-RE to FOLFOX-based chemotherapy plus or minus bevacizumab significantly improved median progression-free survival (PFS) in the liver by 7.9 months (23).

These studies on the role of ^{90}Y-RE in combination with chemotherapy in the first-line treatment of metastatic colorectal cancer have the potential to change the current treatment paradigm. Research is also underway on the use of ^{90}Y-RE in combination with other chemotherapy regimens and systemic therapies, including the use of targeted agents, in other settings. Currently, a phase III trial is underway to compare the effect of ^{90}Y-RE treatment plus modified LV5FU2 chemotherapy plus or minus targeted biologicals (bevacizumab, cetuximab, or panitumumab according to previous use) versus chemotherapy plus or minus targeted agents alone in metastatic colorectal cancer first controlled with induction chemotherapy (clinical trials.gov identifier NCT01895257). A phase I trial has been designed to evaluate the safety of ^{90}Y-RE in combination with the cytotoxic drug TAS-102 in the treatment of chemotherapy refractory metastatic colorectal cancer (clinicaltrials.gov identifier NCT02602327). There is also a published case study on the use of ^{90}Y-RE in combination with FOLFIRI chemotherapy and the anti-angiogenic agent aflibercept in treatment of metastatic colorectal cancer liver metastases. The authors of this case study report that the patient's liver metastases showed partial response, and conclude that this combination therapy was both safe and efficacious in this patient (24).

Such ongoing studies may open up new avenues for the application of ^{90}Y-RE in the treatment of metastatic colorectal cancer liver metastases. As of this moment, however, the majority of patients with metastatic colorectal cancer treated with ^{90}Y-RE are treated with ^{90}Y-RE as monotherapy after multiple lines of failed chemotherapy. The MORE study currently remains the most comprehensive data set involving ^{90}Y-RE treatment in patients after prior failed lines of chemotherapy. Our updated analysis confirms that ^{90}Y-RE treatment provides a meaningful response and survival advantage for MORE patients across all ages and across diverse community and academic centers in the U.S. Overall, this analysis offers reliable information to support ^{90}Y-RE treatment in the eligible metastatic colorectal cancer patients typically seen in most centers, and should help enable proper selection as future patients are treated.

Conclusions

Our updated analysis of the MORE study confirms that ^{90}Y-RE treatment offers favorable survival benefits for patients with unresectable metastatic colorectal cancer patients, even among patients who had received 3 or more prior lines of chemotherapy. Our analysis also confirms earlier reported prognostic factors for survival after ^{90}Y-RE, including number of lines of prior chemotherapy, markers of advanced disease, poor liver function at baseline, pre-treatment anemia, and lung shunt fraction >10%.

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Footnote

Conflicts of Interest: Received research grants from Sirtex Medical (AKennedy, MS, AD); consultant to Sirtex Medical (AD, EW); participant in speakers' bureau for Sirtex Medical (DC, MC, CN); owns stock holdings in Sirtex Medical (AD, SR). SR has also served as a consultant for Surefire Medical, XL Sci-Tech, and Guerbet.

Ethical Statement: Data at each site were collected from source documentation by an independent contract research organization and each site was granted institutional review board exemptions prior to data collection.

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