Unresectable Colorectal Cancer Liver Metastases Treated With Radioembolization: Updated Survival Analysis of the MORE Study

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BACKGROUND

Colorectal cancer is the second leading cause of cancer death in the United States (U.S.) for men and women.[1] In 2016, an estimated 134,490 new cases of colorectal cancers have been diagnosed in the U.S., and of those cases, 49,190 people will die from this disease.[1]

Greater than 50% of patients diagnosed with colorectal cancer either present with liver metastases or go on to develop metastases in the liver.[2] Surgical resection is the treatment of choice for colorectal cancer liver metastases; however, the great majority of such metastases are unresectable upon presentation, and only a percentage are successfully downstaged for surgery by chemotherapy and targeted agents.[2,3] Patients with liver metastases which remain unresectable are generally given second-line chemotherapy, with a poor prognosis and a median survival of approximately one year.[3] For patients who fail chemotherapy, a variety of interventional radiological procedures may also be considered.[4,5,6]

The Metastatic colorectal cancer liver metastases Outcomes after RadioEmbolization (MORE) study (clinicaltrials.gov identifier: NCT01815879) was a retrospective analysis of 606 patients with unresectable colorectal cancer liver metastases treated with radioembolization (RE) using ^{90}Y-labeled resin microspheres (^{90}Y RE). In 2015, the first published safety analysis of this study concluded that ^{90}Y RE was generally well tolerated, with the most common adverse events generally transient and mild in grade. At this time, it was also reported that at a median follow-up of 8.6 months, 503 of the MORE patients had died and overall median survival was 9.6 months.[7] We now report extended survival outcomes of this group through September 2016.

METHODS

Study Design

The MORE study was a retrospective analysis of 606 patients with advanced liver-dominant metastatic colorectal cancer treated with RE using ^{90}Y-labeled resin microspheres (SIR-Spheres®, Sirtex Medical; Sydney, Australia). Patients were consecutively treated between July 2002 and December 2011 at one of 11 experienced RE centers in the U.S. An independent contract research organization collected data from each site. All centers received Institutional Review Board approval for this study.

Patients

Patients were considered for ^{90}Y RE if they had advanced liver-dominant metastatic colorectal cancer which was not suitable for treatment by surgery, systemic therapy, or ablation, and which had progressed or become refractory to at least one line of systemic therapy. Patients received a median of 2 prior lines of systemic chemotherapy (range 0-6) before treatment with ^{90}Y RE alone. 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 this analysis.

Data on baseline characteristics, treatment histories, and adverse events were collected at baseline, at the first ^{90}Y RE treatment, and at all subsequent visits or until death. Survival was calculated from the day of first ^{90}Y RE treatment (day 0) to day of death or last follow-up. Patient medical charts and/or public records were accessed to obtain date of death.

Statistical Analysis

The Kaplan-Meier method was used to estimate overall and stratified survival, and the log-rank test used to determine statistical significance. *P*-values were calculated as follows: for continuous variables, ANOVA; for dichotomous variables, Fisher's exact test; for ordinal variables, Wilcoxon rank sum test; for nominal categorical variables, Chi-Square general association test. Wilcoxon rank sum test was used to calculate *P*-value for prior chemotherapy lines (0, 1, 2, 3+). Fisher's exact test was used to calculate *P*-value for ascites (none vs other).

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	Std 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

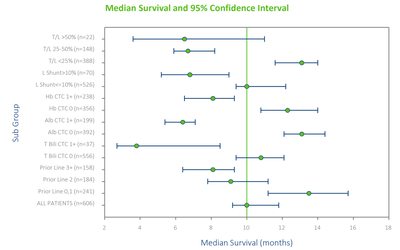

Figure 1. Forest plot of key factors associated with overall survival in patients with metastatic colorectal cancer liver metastases. For each subgroup, the median survival and 95% lower and upper confidence intervals are presented. Vertical line represents the median survival for all patients.

Kaplan-Meier curves of overall patient survival and patient survival stratified by key factors

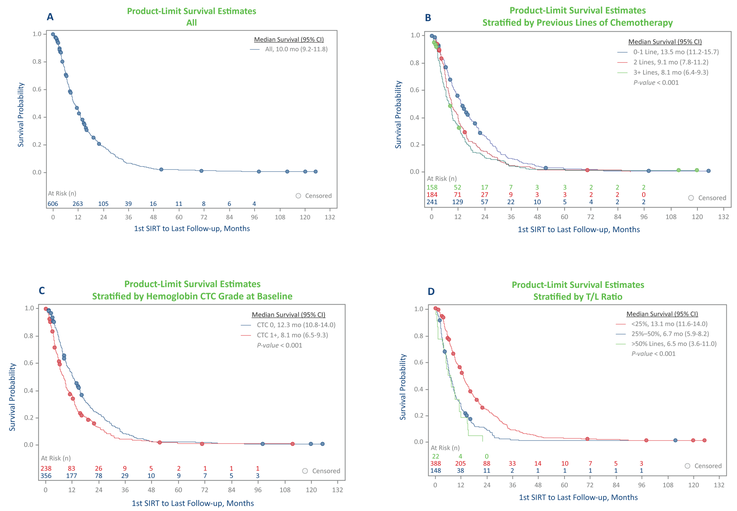

Figure 2. Kaplan-Meier curves of overall patient survival and patient survival stratified by key factors.
Censored observations are represented by circles. Number of patients at risk are provided at yearly intervals. **A.** Survival estimates for all patients. **B.** Survival estimates stratified by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

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

Characteristic	N	Survival, months: Median	95% CI	*P*-values Between Subgroups: *P*-value (log-rank)
All	606	10.0	9.2-11.8	
Sex				0.593
Female	233	9.5	8.9-12.1	
Male	373	10.4	9.1-12.2	
Age				0.261
<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				0.010
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 RE)	184	9.1	7.8-11.2	
3+ (RE 4th-line +)	158	8.1	6.4-9.3	
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				<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.

RESULTS

Extended survival surveillance of patients from the MORE study was conducted through September 15, 2016. During this analysis, we obtained dates of death for an additional 71 patients. The Kaplan-Meier method was used to obtain updated estimates of overall survival for all patients. 45% of patients were still alive one year after ^{90}Y RE treatment; however, less than 10% were alive 3 years after treatment. The updated overall median survival was 10.0 months (95% CI: 9.2-11.8) at a median follow-up of 9.5 months versus 9.6 months (95% CI: 9.0-11.1) at a median follow-up of 8.6 months as reported in the first MORE study analysis.[7]

We also performed an updated analysis of patients examining association of baseline patient characteristics and treatment factors with overall survival. Factors identified as significantly associated with patient survival (P<0.01) are consistent with those identified in the first safety analysis of the MORE study.[7] These factors include increased lines of chemotherapy, poor ECOG performance status, and markers of advanced disease (increased extent of tumor-to-target liver involvement, extra-hepatic metastases, elevated levels of carcinoembryonic antigen [CEA]). Pre-treatment anemia (hemoglobin CTC grade ≥1), lung shunt fraction >10%, and poor baseline liver function were also associated with poor survival (Table 2, Figs 1-2).

CONCLUSIONS

Long-term follow-up confirms originally reported prognostic factors for survival. Median survival times of patients compares favorably with that of patients treated with systemic therapies in similar settings.[7,8,9,10] We conclude that ^{90}Y radioembolization offers a favorable survival benefit for patients with unresectable colorectal cancer liver metastases, even among those who already received 3 or more lines of chemotherapy.

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