Original Article

Multicenter evaluation of the safety and efficacy of radioembolization in patients with unresectable colorectal liver metastases selected as candidates for ^{90}Y resin microspheres

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Background: Metastatic colorectal cancer liver metastases Outcomes after RadioEmbolization (MORE) was an investigator-initiated case-control study to assess the experience of 11 US centers who treated liver-dominant metastases from colorectal cancer (mCRC) using radioembolization [selective internal radiation therapy (SIRT)] with yttrium-90-(^{90}Y)-labeled resin microspheres.

Methods: Data from 606 consecutive patients who received radioembolization between July 2002 and December 2011 were collected by an independent research organization. Adverse events (AEs) and survival were compared across lines of treatment using Fisher's exact test and Kaplan-Meier estimates, respectively.

Results: Patients received a median of 2 (range, 0-6) lines of prior chemotherapy; 35.1% had limited extrahepatic metastases. Median tumor-to-liver ratio and -activity administered at first procedure were 15% and 1.17 GBq, respectively. Hospital stay was <24 hours in 97.8% cases. Common grade ≥3 AEs over 184 days follow-up were: abdominal pain (6.1%), fatigue (5.5%), hyperbilirubinemia (5.4%), ascites (3.6%) and gastrointestinal ulceration (1.7%). There was no statistical difference in AEs across treatment lines (P>0.05). Median survivals [95% confidence interval (CI)] following radioembolization as a 2nd-line, 3rd-line, or 4th-plus line 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; and significantly prolonged in patients with ECOG 0 *vs.* ≥1 (P=0.009). Statistically significant independent variables for survival at radioembolization were: disease stage [extrahepatic metastases, extent of liver involvement (tumor-to-treated-liver ratio)], liver function (uncontrolled ascites, albumin, alkaline phosphatase, aspartate transaminase), leukocytes, and prior chemotherapy.

Conclusions: Radioembolization appears to have a favorable risk/benefit profile, even among mCRC patients who had received ≥3 prior lines of chemotherapy.

Keywords: Yttrium-90 (^{90}Y); brachytherapy; salvage therapy; albumin; alkaline phosphatase; ascites; bilirubin

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Introduction

In 2013, there were an estimated 142,820 new cases and 50,830 deaths due to colorectal cancer (CRC) in the United States (1). Liver metastases are common among patients with metastatic CRC (mCRC), and while surgical resection of these tumors is the treatment of choice, anatomical factors (such as location or extent of metastatic lesions), inadequate hepatic functional reserve, or comorbidities render approximately 75-90% of patients ineligible for resection (1). For patients with unresectable liver metastases, there are several locoregional liver-directed treatment options available.

One such liver-directed treatment is radioembolization [RE; also termed selective internal radiation therapy (SIRT)] with yttrium-90-labeled (^{90}Y) microspheres (2). This treatment modality utilizes the well-characterized dual vasculature of the liver to selectively deliver radioactive isotopes to liver tumors via the hepatic artery. The feasibility of transarterial ^{90}Y-RE to treat liver metastases was first described in 1965 (3), and since then, there have been numerous published studies of its effectiveness in both primary and metastatic liver tumors (4). In prospective clinical studies, RE with ^{90}Y resin microspheres improved response rates in the liver and extended time to progression and overall survival (OS), relative to chemotherapy alone, in both the first-line and refractory setting (5-8) among patients with mCRC. Metastatic colorectal cancer liver metastases Outcomes after RadioEmbolization (MORE) was a retrospective study designed to evaluate the safety and OS associated with ^{90}Y-RE in patients with mCRC, based on the collective experience of centers in the United States.

Methods and materials

Study design

This was an investigator-initiated study (clinicaltrials.gov identifier: NCT01815879). Fifteen of the most experienced radioembolization centers using ^{90}Y-resin microspheres in the United States were invited by the principal investigator to participate in this retrospective review, and 11 of these centers accepted. Institution review board exemptions were granted prior to the collection of data at each site. All patients with a diagnosis of mCRC who received at least one radioembolization procedure were followed-up and included in the analyses. Data were collected from source documentation at each site by an independent contract research organization. All patient identifiers were replaced with a unique study number.

Centers were guided by the published consensus from the Radioembolization Brachytherapy Oncology Consortium (REBOC) and other earlier reviews in the selection of patients, pre-treatment work-up and dosimetry (2,9,10). In summary, ^{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 (11,12).

Radioembolization

The technique and rationale for the various procedures involved with delivering radioactive ^{90}Y resin microspheres (SIR-Spheres; Sirtex Medical Ltd, Sydney, Australia) into the hepatic artery are well described elsewhere (2). It was the treating physician's preference whether to treat lobar or bilobar disease in a single session. All activity calculations for ^{90}Y were planned using the body surface area methodology as per consensus guidelines. Clinical judgment was used to assess the appropriateness of RE in patients presenting with relative contraindications including compromised pulmonary function, ascites or inadequate liver reserve.

Data collection and analysis

Safety data were collated from the medical records at baseline, on the day of the first ^{90}Y-RE procedure (day 0), and at all subsequent visits or until death. All results from hematologic, liver function and blood biochemistry tests and physical examination were recorded. The nature and severity of all adverse events (AEs) were graded using the National Cancer Institute Common Toxicity Criteria Adverse Events version 3.0 (13). Data were reported on the time and highest grade across each of the following time-points: days 0, 1-7, 8-90 and 91-184 and any time-point. Survival was calculated from the day of the first ^{90}Y-RE procedure to the day of death or last follow-up. Patients were censored at the time of last follow up if their status could not be established.

Statistical methodology

Summary statistics for continuous variables include the mean, median, standard deviation, interquartile range (IQR), minimum and maximum, and 95% confidence intervals (CI), as appropriate. Categorical data are summarized by frequency distributions with percentage based on non-

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missing data. Descriptive summaries are provided for baseline patient characteristics, prior chemotherapy history, ^{90}Y treatments and AEs. The association of Grade 3+ AEs or death and lines of prior chemotherapy (1,2,3-6) utilized Fisher's exact test. Overall and stratified survival were estimated by the method of Kaplan and Meier (14) and the Log rank test was used to assess statistical significance. Univariate Cox proportional hazards models were applied to identify univariate prognostic factors associated with survival and a multivariate proportional hazards model was applied to the statistically significant univariate variables by either Kaplan-Meier or Cox proportional hazards models. The analysis model was constructed based on the maximum number of statistically significant variables. Statistical significance was determined at 2-sided alpha 0.05, and no adjustments were made for multiple comparisons. All statistical analyses were conducted using SAS (SAS, Cary, NC, USA) version 9.2 XP Pro statistical analysis software.

Results

Patient characteristics and prior treatment

Between July 2002 and December 2011, 606 consecutive patients with mCRC were treated with ^{90}Y-RE at the 11 participating centers (*Table 1*,*S1*) and followed up over a median of 8.6 (range, 0.1-77.7) months from first radioembolization procedure (day 0). During this time, a total of 503 deaths were recorded. Candidates for ^{90}Y-RE had either had liver-only (64.9%) or limited extra-hepatic metastases with an indolent clinical course (35.1%); a few patients had the primary *in situ* (13.0%).

Patients had received a median of 2 prior lines of systemic chemotherapy (range, 0-6) for the treatment of mCRC, consisting mostly of fluoropyrimidine-based treatment combined with oxaliplatin or irinotecan with or without bevacizumab (1st or 2nd-line) and an EGFR inhibitor (3rd-line) (see *Table S2*). After systemic chemotherapy for mCRC, 206 patients (35.3%) received ^{90}Y-RE second-line (after one prior line of chemotherapy), 184 (31.6%) ^{90}Y-RE 3rd-line (after two prior lines), and 158 patients (27.1%) ^{90}Y-RE fourth-plus line (after three or more prior lines).

Treatment target and design

A median of two ^{90}Y-RE procedures (IQR: 1.0) were conducted for each patient. Hospital stay was <24 hours in 97.8% of cases. The treatment volume (whole-liver, lobar or segmental) and design (i.e., sequence of treatments) are outlined in *Table S3*. Most patients (93.2%) received ^{90}Y-RE as either 1 (49.7%) or 2 (43.6%) procedures, mainly targeting either the whole liver (65.7%) or right lobe (27.7%). For 219 (36.1%) patients who received whole-liver treatment using a sequential lobar approach, ^{90}Y-RE of both lobes occurred within a 10-week timeframe in 84.5% of cases; the right lobe was determined to be the dominant diseased lobe and was treated before the left lobe in 86.7% of cases (see *Table S3*). Of 179 (29.5%) patients who received initial whole-liver treatment, retreatment of partial or whole liver occurred in 26.8%. The median tumor-to-target-liver ratio for the first ^{90}Y-RE therapy was 15% (IQR: 18%) (see *Table S4*), while the median overall tumor-to-target-liver ratio considering sequential treatment of bilobar disease and/or subsequent ^{90}Y-RE was 15% (IQR: 21%). Patients received a median of 1.17 GBq (IQR: 0.49) of ^{90}Y activity for the first procedure, which was greater than for any subsequent ^{90}Y-RE procedure. A median of 1.46 (range, 0.11-5.51) GBq of total ^{90}Y activity was delivered to patients across all treatments. Correspondingly, compared to the initial procedure, the median treated liver and tumor volumes were approximately halved (46.8% and 57.3%, respectively) during the second procedure, reflecting the predominant technique of treating whole-liver or right lobe in the first session, and left lobe subsequently. Post-^{90}Y-RE only a minority of patients continued to receive chemotherapy, based on the available data (see *Table S5*).

Safety and tolerability

AEs were monitored from the day of the first ^{90}Y-RE procedure up to 184 days (6 months) in all 606 patients. All-cause cumulative mortality was 12 (2.0%) on day 30, 37 (6.1%) on day 60 and 85 (14.0%) on day 90 after the procedure.

Common AEs were usually mild (grade 1/2) and included: fatigue (all grades: 43.7%; grade ≥3: 5.8%), abdominal pain (39.3%; 6.1%), nausea (28.4%; 1.3%) and vomiting (10.6%; 1.5%) (*Table 2*,*S6*). These events appeared within the first week of treatment, and were mainly transient and managed with medication, as necessary.

Gastrointestinal ulcerations (all grades: 3.5%) was severe (grade ≥3) in 1.7% of patients and may have contributed to the death of one (0.2%) patient. There were 3 recorded cases among 606 (0.5%) patients of grade ≥3 radioembolization-induced liver disease (REILD) and 2 further cases of

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Table 1 Baseline patient and disease characteristics, and prior procedures (N=606)

Parameter	Data
Gender, N (%)	
Female	233 (38.4)
Male	373 (61.6)
Age, mean ± SD (range) (years)	61.5±12.7 (20.8-91.9)
Race, N (%)[xiv]	
White or Caucasian	398 (77.7)
Black or African American	67 (13.1)
Hispanic or Latino	17 (3.3)
Asian	12 (2.3)
Other	18 (3.5)
ECOG performance status, N (%)[xvi]	
0	168 (65.4)
1	72 (28.0)
2	14 (5.4)
3	3 (1.2)
Site of primary, N (%)[i]	
Colon	443 (73.3)
Rectum	133 (22.0)
Colorectal	28 (4.6)
Primary tumor *in situ*, N (%)[iii]	78 (13.0)
Metastases (%)[xi*]	
Synchronous	396 (69.6)
Extrahepatic metastases, N (%)	
Yes	213 (35.1)
No	393 (64.9)
Lung	148 (24.4)
Lymph node	67 (11.1)
Peritoneum	17 (2.8)
Bone	30 (5.0)
Other	38 (6.3)
Carcinoembryonic antigen, median (IQR) (μg/L)[xv]	62.2 (283.4)
Ascites, N (%)[vii]	
Yes	28 (4.7)
Prior liver-directed procedures, N (%)	
Any	183 (30.2)
Surgery and/or ablation	168 (27.7)
Vascular therapy (HAI, TACE, TAE)	37 (6.1)
Upper abdominal radiation	7 (1.2)
Stereotactic external beam radiotherapy	4 (0.7)
Prior lines of systemic chemotherapy for mCRC, N (%)	
None (^{90}Y-RE at 1st-line)	35 (6.0)
1 line (^{90}Y-RE at 2nd-line)	206 (35.3)
2 lines (^{90}Y-RE at 3rd-line)	184 (31.6)
≥3 lines (^{90}Y-RE at ≥4th-line)	158 (27.1)
Unknown	23 (3.8)
Time from mCRC diagnosis to RE, median (range) (months)[x]	16.3 (0.4-96.3)
Albumin, median (IQR) (g/dL)[viii]	3.7 (0.8)
Total bilirubin, median (IQR) (mg/dL)[vi]	0.6 (0.5)
Alkaline phosphatase, median (IQR) (U/L)[vii]	146.0 (143.0)
Alanine transaminase, median (IQR) (U/L)[x]	30.0 (24.0)
Aspartate aminotransferase, median (IQR) (U/L)[ix]	35.0 (29.0)
Creatinine, median (IQR) (mg/dL)[iv]	0.9 (0.3)
Hemoglobin, median (IQR) (g/dL)[v]	12.4 (2.6)
Platelets, median (IQR) (×10^9/L)[iv]	213.0 (121.0)
Neutrophils, median (IQR) (×10^9/L)[xviii]	4.1 (2.1)
Lymphocytes, median (IQR) (×10^9/L)[xvii]	1.2 (0.7)
Tumor-to-target liver involvement at first ^{90}Y-RE, median (range) (%)[xiii]	15% (0.1-100)
Tumor-to-target liver at first ^{90}Y-RE, N (%)[xiii]	
<25%	388 (69.5)
25-50%	148 (26.5)
>50%	22 (3.9)
Overall tumor-to-target liver involvement, median (range) (%)[xii]	15% (0.1-100)
Treated target, N (%)[i]	
Whole-liver, single-session ± retreatment	179 (29.5)
Whole-liver, sequential	218 (36.0)
Right lobe ± segmental	168 (27.7)
Left lobe ± segmental	33 (5.4)
Segmental	5 (0.8)
Activity administered, median (range) (GBq)[ii]	
First treatment	1.17 (0.11-2.29)
All treatments	1.46 (0.11-5.51)

Missing patient baseline data on: [i], 2 patients; [ii], 4 patients; [iii], 6 patients; [iv], 11 patients; [v], 12 patients; [vi], 13 patients; [vii], 15 patients; [viii], 16 patients; [ix], 22 patients; [x], 29 patients; [xi], 37 patients; [xii], 47 patients; [xiii], 48 patients; [xiv], 94 patients; [xv], 176 patients; [xvi], 349 patients; [xvii], 458 patients; [xviii], 479 patients; *, synchronous defined as the identification of metastases within 4 months (120 days) of the primary. HAI, hepatic arterial infusion chemotherapy; TACE, transarterial chemoembolization; TAE, transarterial embolization; IQR, interquartile range.

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Table 2 Common (≥1% or recognized potential complications)* all-causality adverse events by severity (CTCAE v3 grade) from first ^{90}Y-RE procedure (day 0) in 606 patients

System organ, class	Any time point, days 0-184, N (%)		
	Unknown	CTCAE grade 1-2	CTCAE grade ≥3
Gastrointestinal	3 (0.5)	251 (41.4)	62 (10.2)
Abdominal pain	1 (0.2)	200 (33.0)	37 (6.1)
Nausea	5 (0.8)	159 (26.2)	8 (1.3)
Vomiting	0	55 (9.1)	9 (1.5)
Gastrointestinal ulcer	1 (0.2)	10 (1.7)	10 (1.7)
Abdominal distension	0	16 (2.7)	2 (0.3)
Dyspepsia	0	20 (3.3)	0
Gastritis	0	3 (0.5)	3 (0.5)
Duodenitis	0	1 (0.2)	1 (0.2)
Intestinal obstruction	1 (0.2)	2 (0.3)	4 (0.7)
Constipation	2 (0.4)	18 (2.9)	0
Diarrhea	0	9 (1.5)	0
Flatulence	0	6 (1.0)	0
Constitutional	7 (1.2)	241 (39.8)	39 (6.4)
Fatigue	4 (0.7)	228 (37.6)	33 (5.5)
Fever	2 (0.4)	43 (7.1)	2 (0.3)
Weight loss	1 (0.2)	11 (1.8)	0
Peripheral edema	3 (0.5)	3 (0.5)	4 (0.7)
Psychiatric	3 (0.5)	42 (6.9)	5 (0.8)
Anorexia nervosa	3 (0.5)	41 (6.8)	5 (0.8)
Hepatobiliary	1 (0.2)	69 (11.4)	52 (8.6)
Hyperbilirubinemia	1 (0.2)	61 (10.1)	31 (5.1)
Ascites	2 (0.3)	11 (1.8)	17 (2.8)
Radioembolization-induced liver disease	5 (0.8)	2 (0.3)	3 (0.5)
Cholecystitis	0	5 (0.8)	2 (0.3)
Hepatic failure	2 (0.3)	2 (0.3)	2 (0.3)
Musculoskeletal	1 (0.2)	17 (2.8)	1 (0.2)
Back pain	0	7 (1.2)	0
Vascular disorders	2 (0.3)	7 (1.2)	7 (1.2)
Respiratory	2 (0.3)	19 (3.1)	2 (0.3)
Influenza	1 (0.2)	10 (1.6)	0

*, This table reports the highest grade of adverse event reported by each patient at any time interval from days 0-184.

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grade ≥3 hepatic failure (total 5/606; 0.8%); all events occurred between 8-90 days following the first treatment and all patients subsequently died. More detailed analysis of these patients found that all were Caucasians; none had prior surgery or other liver-directed treatment. ^{90}Y-RE was administered as a single whole-liver treatment (1 patient) or sequential lobar treatment (1 patient); or only to the right lobe (2 of 3 patients with reported REILD). Four of the five patients (including all three patients with REILD) had disease which had advanced beyond the liver to the lungs, as well as one other site (lymph, spleen or bone) in three patients; two patients had ascites at baseline and therefore were outside of the normally accepted eligibility criteria.

Analyses of baseline laboratory parameters revealed that a high proportion of patients had mild-to-moderate (mostly grade 1 or 2) changes before ^{90}Y-RE including: alkaline phosphatase (all grades: 59.3%; grade 3: 3.0%); AST (49.8%; 1.5%), albumin (33.7%; 1.4%) and hemoglobin (40.1%; 0.7%). The proportion of patients with mild asymptomatic increases in hepatic enzymes level rose during the 90 days post-treatment, but these changes were mostly transient. The incidence of any clinically significant grade ≥3 change in liver function tests is recorded in the *Table S*7. Raised total bilirubin (all grades; all causality including liver progression) was recorded in 6.2% of patients at baseline, increasing to 22.6% of patients by day 90 following the first treatment, with a minority experiencing grade 3 (4.9%) or 4 (2.7%) events at day 90.

Analyses found no correlation between the number of lines of prior chemotherapy and the reporting of severe (grade ≥3) AEs over the 90 days after the first ^{90}Y-RE procedure (P>0.05 by Fisher's Exact Test). The incidence of all grade ≥3 hepatobiliary events was similar regardless of whether patients had received prior chemotherapy or not (P=1.00). Grade ≥3 events such as fatigue (5.6% *vs.* 2.9%), abdominal pain (6.5% *vs.* 0%) and hyperbilirubinemia (5.3% *vs.* 2.9%) were more frequently reported in patients who had received prior chemotherapy compared to the chemotherapy-naïve sub-group, although the difference was not statistically significant.

Survival analyses

The median OS in 606 patients was 9.6 months (95% CI: 9.0-11.1), which did not differ significantly by gender, race or age (*Table S8*). Analyses of patients treated with radioembolization over a decade found that survival did not differ significantly across time periods.

Median survival was significantly prolonged in patients with ECOG ps 0 at baseline compared with ECOG ≥1 (P=0.009); in patients without extra-hepatic metastases compared with those with extra-hepatic metastases (P<0.001); in patients who were considered eligible for retreatment with ^{90}Y-RE more than 90 days after the first procedure compared with those who were not (P<0.001); and in patients who had received at least three ^{90}Y-RE procedures (P<0.005) (*Table 3*).

Median survivals (95% CI) differed significantly between patients receiving ^{90}Y-RE as a 2nd-, 3rd-, and 4th+ line of treatment after chemotherapy: 13.0 months (95% CI: 10.5-14.6), 9.0 months (95% CI: 7.8-11.0), and 8.1 months (95% CI: 6.4-9.3), respectively (P<0.001) (*Figure 1*). Median survival in patients with unknown prior lines of chemotherapy (N=23) was 13.1 months (95% CI: 4.1-14.4). For the highly heterogeneous sub-group of patients who had received no prior chemotherapy, survival differed significantly by age: younger patients (<75 years) survived a median of 25.2 months (95% CI: 9.3-36.5) compared with 11.9 months (95% CI: 4.0-15.6) in patients aged ≥75 years.

Survival was similar in patients who had received prior liver-directed surgery or ablation compared to those who had not (*P*=0.067). Survival was also significantly determined by the severity of liver dysfunction before ^{90}Y-RE (*Table 3*,*S8*).

Upon multivariate analysis, statistically significant independent variables for survival at the time of ^{90}Y-RE were: disease stage [extrahepatic metastases, extent of liver involvement (tumor-to-treated-liver ratio)] and liver function (uncontrolled ascites, albumin, ALP, AST) and white blood cell count as well as prior lines of chemotherapy (*Table S9*).

Discussion

This study describes the risks and benefits of RE using ^{90}Y-resin microspheres in the largest analysis ever conducted in patients receiving RE for any tumor type. The data paint a picture of a cohort of patients who, despite a wide-ranging intensity and duration of prior chemotherapy for mCRC, had a similar stage of disease (i.e., predominately localized to the liver) at the point when treatment with ^{90}Y-RE was initiated. Despite this, we found that differences in the extent of disease in the liver (tumor-to-treated-liver ratio) and beyond (EHD), as well as baseline liver function (as measured by ascites and liver function tests) and extent of prior chemotherapy, all were significant predictors of

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Table 3 Kaplan-Meier analysis of survival by baseline characteristics

Characteristic	Survival, months[†]			
	N	Median	95% CI	P value
All	606	9.6	9.0-11.1	NA
ECOG performance status				0.009[i]
0	168	11.2	9.1-13.1	
1	72	8.1	6.4-11.0	
2	14	6.0	2.3-12.2	
3	3	5.0	1.3-11.0	
Extra-hepatic metastases				<0.001
No	393	12.1	10.8-13.6	
Yes	213	7.4	6.1-8.5	
Primary tumor *in situ*				0.016
No	522	10.0	9.1-11.8	
Yes	78	8.1	6.2-10.4	
Ascites				<0.001[ii]
No	563	10.0	9.2-11.8	
Yes (controlled)	5	2.4	0.7-22.9	
Yes (uncontrolled)	23	5.5	3.6-7.4	
Prior lines of chemotherapy				<0.001
RE 2nd-line	206	13.0	10.5-14.6	
RE 3rd-line	184	9.0	7.8-11.0	
RE 4th-line +	158	8.1	6.4-9.3	
RE 1st-line				0.041
All	35	13.5	7.2-17.1	
<75 years	17	25.2	9.3-36.5	
≥75 years	18	11.9	4.0-15.6	
Number of ^{90}Y-RE procedures				0.005[iii]
1	301	8.9	7.7-10.8	
2	264	9.6	8.6-11.2	
3	29	17.7	11.2-23.7	
4	10	19.0	9.3-25.4	
5	2	28.1	26.4-29.8	
1st to 2nd ^{90}Y-RE procedure >90 days				<0.001
No	58	18.3	15.8-23.1	
Yes	246	9.2	8.1-9.9	
Tumor-to-target liver involvement				<0.001
<25%	388	12.8	10.8-13.6	
25-50%	148	6.5	5.7-8.1	
>50%	22	6.0	3.6-9.1	
Carcinoembryonic antigen				<0.001
< median	215	13.6	12.2-16.3	
≥ median	215	7.4	6.6-8.5	
Total bilirubin, CTC grade				<0.001
0	556	10.4	9.3-11.9	
≥1	37	3.8	2.5-7.4	
Albumin, CTC grade				<0.001
0	392	13.0	11.6-13.9	
≥1	199	6.3	5.4-7.1	
Alkaline phosphatase, CTC grade				<0.001
0	241	15.7	13.9-17.7	
≥1	351	7.1	6.3-8.1	
Aspartate aminotransferase, CTC grade				<0.001
0	296	13.9	12.2-15.6	
≥1	294	7.2	6.3-8.7	
Creatinine, CTC grade				0.041
0	569	9.6	9.0-11.2	
≥1	26	7.1	4.7-12.2	
Hemoglobin, CTC grade				<0.001
0	356	12.2	10.6-13.6	
≥1	238	7.6	6.4-9.0	

P values for continuous variables by one-way ANOVA; P values for dichotomous variables by Fisher's exact test, and P values for nominal categorical variables by Chi-Square general association test. [†], median survival calculated by Kaplan-Meier analysis; [i], P value: ECOG ps 0 *vs.* 1 *vs.* 2-3; [ii], P value: ascites (not controlled) *vs.* ascites (controlled) or none; [iii], P value: RE procedures 1 *vs.* 2 *vs.* 3-5. CI, confidence interval; NA, not applicable.

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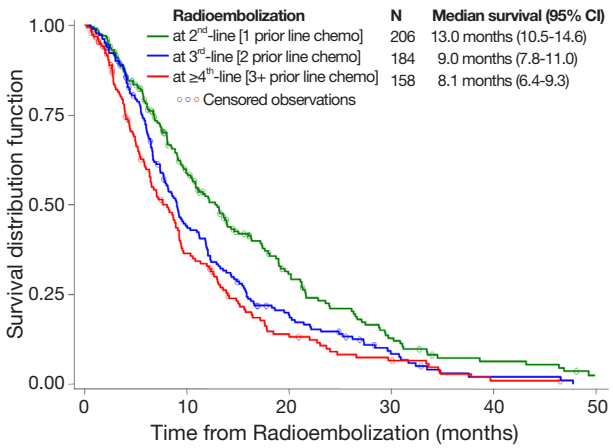

Figure 1 Kaplan-Meier survival curves of patients with mCRC following radioembolization using ^{90}Y resin microspheres stratified by treatment setting for ^{90}Y RE relative to prior chemotherapy lines. mCRC, metastatic CRC.

survival.

Radiation damage (REILD) to normal liver reserve is always a concern and guides careful ^{90}Y activity selection and catheter placement. The incidence of REILD in this cohort is the lowest of any study of mCRC patients to date (5,8,15,16). In the majority of patients, REILD is transient and not fatal; however a few deaths have been reported in patients with progressive liver failure attributed to REILD and not tumor progression (5,8,15,16). The etiology of REILD is not known, with contradictory evidence published regarding increased risk related to: volume of liver irradiated, total activity of radiation delivered, prior partial hepatectomy, prior ablative liver therapy, and amount of prior chemotherapy exposure. The Pamplona group have shown that multiple lines of prior chemotherapy is a risk factor for REILD; however, analyses of our data found no correlation between the number of lines of prior chemotherapy (nor any one chemotherapy regimen) and the incidence of severe (grade ≥3) AEs after ^{90}Y-RE (17,18).

Median survival following ^{90}Y-RE was 13.0 months in the 2nd-line setting after chemotherapy which compares well to similar patients receiving 2nd-line chemotherapy combined with aflibercept (median 13.5 months) (19), and bevacizumab beyond progression (median 11.2 months) (20). The median survival of 9.0 and 8.1 months following ^{90}Y-RE in patients with 2 or ≥3 prior lines of chemotherapy, respectively, in this study compares favorably with patients treated in a similar setting using regorafenib or placebo (median 6.4 *vs.* 5.0 months) (21). The data also point to a sub-cohort of long-term survivors who had already survived a median of 25.6 months (and had received a median of ≥3 lines of chemotherapy) since diagnosis of mCRC and were still eligible for ^{90}Y-RE. Although twice as likely to have metastases beyond the liver and adverse prognostic clinical markers such as ascites and elevated alkaline phosphatase, these patients remarkably survived a median of 8.1 months after ^{90}Y-RE (i.e., a median OS of 34 months since diagnosis of mCRC compared with a median survival of 24 months since diagnosis of mCRC in patients who were at a similar stage of disease after one line of chemotherapy). These differences can be attributed in part to the tumor biology of the patients selected as candidates for this treatment.

In conclusion, the evidence from this study show that even among patients who were heavily pre-treated, ^{90}Y-RE appears to have a favorable risk/benefit profile and offer clinicians a more targeted approach for the management of liver-dominant mCRC.

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Supplementary Tables

Table S1 Baseline patient and disease characteristics according to the setting of ^{90}Y-RE relative to prior lines of mCRC chemotherapy

Parameter	1st-line ^{90}Y-RE (N=35)	2nd-line ^{90}Y-RE (N=206)	3rd-line ^{90}Y-RE (N=184)	4th+ line ^{90}Y-RE (N=158)	Unknown (N=23)
Gender, N (%)					
Female	14 (40.0)	74 (35.9)	67 (36.4)	71 (44.9)	7 (30.4)
Male	21 (60.0)	132 (64.1)	117 (63.6)	87 (55.1)	16 (69.6)
Age (years)					
mean ± SD (range)	71.6±12.4 (33.6-91.9)[†]	60.7±12.6 (30.0-89.2)	61.5±12.0 (30.0-84.3)	60.7±11.9 (33.5-88.1)	58.5±16.9 (20.8-85.1)
≥70 (%)	21 (60.0)	50 (24.3)	46 (25.0)	37 (23.4)	6 (26.1)
≥75 (%)	17 (48.6)	30 (14.6)	26 (14.1)	21 (13.3)	3 (13.0)
ECOG performance status, N (%)					
0	6 (50.0)[xiii]	44 (61.1)[xvi]	60 (65.9)[xv]	57 (70.4)[xiv]	1[xii]
1	3 (25.0)	25 (34.7)	25 (27.5)	19 (23.5)	0
2	3 (25.0)	3 (4.2)	5 (5.5)	3 (3.7)	0
3	0	0	1 (1.1)	2 (2.5)	0
Primary tumor *in situ*, N (%)					
Yes	1 (2.9)[i,§]	35 (17.2)[ii,§]	18 (9.8)[§]	19 (12.1)[i,§]	5 (23.1)[ii,§]
Extrahepatic metastases, N (%)					
Yes	7 (20.0)[‡]	55 (26.7)[‡]	67 (36.4)[‡]	79 (50.0)[‡]	5 (21.7)[‡]
Ascites, N (%)					
Yes	1 (2.9)	7 (3.5)[iv]	8 (4.4)[iv]	12 (7.9)[v]	0[ii]
Controlled	1 (2.9)	2 (1.0)	1 (0.6)	1 (0.7)	0
Uncontrolled	0	5 (2.5)	7 (3.9)	11 (7.2)	0
Prior liver-directed procedures, N (%)					
Surgery and/or ablation	4 (11.4)	56 (27.2)	56 (30.4)	50 (31.6)	2 (8.7)
Vascular therapy	0[‡]	2 (1.0)[‡]	8 (4.3)[‡]	27 (17.1)[‡]	0[‡]
Time since identification of mCRC to RE, Median (range) (months)	1.8 (0.4-20.9)[i,‡]	11.5 (0.9-69.3)[vi,‡]	20.1 (0.7-96.3)[ix,‡]	26.0 (4.0-90.6)[ix,‡]	8.6 (3.5-59.8)[iv,‡]
Tumor-to-target liver ratio, median (range) (%)	15 (0.9-71)[iv]	15 (0.1-100)[xi]	12 (0.3-78)[x]	15 (0.2-100)[x]	28 (1.7-60)[i]
Tumor-to-target liver, N (%)					
<25%	23 (74.2)[iv]	132 (70.6)[xi]	126 (73.3)[x]	97 (66.4)[x]	10 (45.5)[i]
25-50%	5 (16.1)	48 (25.7)	43 (25.0)	41 (28.1)	11 (50.0)
>50%	3 (9.7)	7 (3.7)	3 (1.7)	8 (5.5)	1 (0.5)
Albumin (g/dL)					
Median (IQR)	3.8 (0.6)	3.7 (0.7)[vii]	3.7 (0.7)[vii]	3.6 (0.8)	3.6 (1.3)
CTC grade ≥1, N (%)	9 (25.7)	66 (33.2)	51 (28.8)	64 (40.5)	9 (40.9)
Total bilirubin (mg/dL)					
Median (IQR)	0.7 (0.3)[§]	0.6 (0.4)[vii,§]	0.7 (0.4)[v,§]	0.7 (0.5)[§]	0.7 (0.5)[§]
CTC grade ≥1, N (%)	0	10 (5.0)	12 (6.7)	13 (8.2)	2 (9.1)
Alkaline phosphatase (U/L)					
Median (IQR)	116.0 (124.0)[‡]	123.5 (111.0)[viii,‡]	147.0 (131.0)[iv,‡]	187.0 (192.0)[i,‡]	136.5 (115.0)[‡]
CTC grade ≥1, N (%)	17 (48.6)[‡]	96 (48.5)[viii,‡]	113 (62.8)[iv,‡]	112 (71.3)[i,‡]	13 (59.1)[‡]
Number of ^{90}Y-RE procedures, N (%)					
1	17 (48.6)	101 (49.0)	83 (45.1)	88 (55.7)	12 (52.2)[i]
2	15 (42.9)	89 (43.2)	88 (47.8)	61 (38.6)	11 (47.8)
3	2 (5.7)	12 (5.8)	10 (5.4)	5 (3.2)	0
4	1 (2.9)	3 (1.5)	3 (1.6)	3 (1.9)	0
5	0	1 (0.5)	0	1 (0.6)	0

Missing patient baseline data on: [i], 1 patient; [ii], 2 patients; [iii], 3 patients; [iv], 4 patients; [v], 5 patients; [vi], 6 patients; [vii], 7 patients; [viii], 8 patients; [ix], 9 patients; [x], 12 patients; [xi], 19 patients; [xii], 22 patients; [xiii], 23 patients; [xiv], 77 patients; [xv], 93 patients; [xvi], 134 patients; [§], P<0.05 across sub-groups; [‡], P<0.001 across sub-groups; [†], P< 0.001 compared to other sub-groups.

Table S2 Prior systemic chemotherapy history for mCRC

Prior agents	^{90}Y-RE setting relative to prior chemotherapy lines, N (%)		
	2nd-line ^{90}Y-RE (N=206)	3rd-line ^{90}Y-RE (N=184)	4th+ line ^{90}Y-RE (N=158)
Fluoropyrimidine	185 (89.8)	177 (96.2)	155 (98.1)
Oxaliplatin	148 (71.8)	152 (82.6)	150 (94.9)
Irinotecan	27 (13.1)	124 (67.4)	145 (91.8)
Any biologic agent	141 (68.4)	151 (82.1)	148 (93.7)
Bevacizumab	132 (64.1)	139 (75.5)	133 (84.2)
EGFR inhibitor	12 (5.8)	44 (23.9)	109 (69.0)
TKI inhibitors	0	1 (0.5)	7 (4.4)
Unspecified agent(s)	16 (7.8)	21 (11.4)	14 (8.9)
Other agents	3 (1.5)	5 (2.7)	13 (8.2)

Table S3 Treatment target and design

Treated target	Design (sequence)	Total number of ^{90}Y-RE procedures per patient, N (%)					
		1 (N=301)	2 (N=264)	3 (N=29)	4 (N=10)	5 (N=2)	Total
Whole liver							
Total		131	231	26	8	2	398 (65.7)
Single session	Whole-liver, single session ± retreatment (partial or whole)	131	45	1	1	1	179 (29.5)
Sequential (<10 weeks)	Right lobe before left lobe or whole liver (<10 weeks†)		143	15	5	1	164 (27.1)
	Left lobe before right lobe or whole liver (<10 weeks†)		20	4	1		25 (4.1)
Sequential (≥10 weeks)	Right lobe before left lobe or whole liver (≥10 weeks†)		18	4			22 (3.6)
	Left lobe before right lobe or whole liver (≥10 weeks†)		4	2	1		7 (1.2)
Sequential (unknown)	Right lobe before left lobe (interval unknown)		1				1 (0.2)
Partial liver	Right lobe ± segmental	140	24	3	1		168 (27.7)
	Left lobe ± segmental	26	6		1		33 (5.4)
	Segmental	4	1				5 (0.8)
Unknown	Right lobe + left or unknown target segment		2				2 (0.3)
Total		301 (49.7)	264 (43.6)	28 (4.6)	10 (1.7)	2 (0.3)	606 (100.0)

†, denotes the interval between first and second treatments in patients receiving sequential lobar ^{90}Y-RE.

Table S4 Radioembolization treatment characteristics by number of ^{90}Y-RE treatments performed

Parameter	^{90}Y-RE treatments				
	1	2	3	4	5
Patients treated, N	606	305	41	12	2
Lung shunt (%), median (range)	4.9 (0.02-45.0)[viii]	4.7 (0.02-22.5)[xviii]	5.95 (1.1-19.0)[vii]	7.8 (2.0-11.4)[iv]	7.75 (5.9-9.6)
Embolization of non-target arteries, N (%)	499 (82.5)[i]	58 (19.1)[ii]	4 (10.0)[i]	4 (33.3)	2 (100.0)
Dosimetry method					
BSA formula	554 (97.0)	271 (94.8)	38 (100.0)[iii]	12 (100.0)	2 (100.0)
Empiric method	17 (3.0)[xv]	15 (5.2)[xii]	0	0	0
Planned treatment approach, N (%)					
Whole liver	179 (29.5)	41 (13.4)	5 (12.2)	1 (8.3)	0
Right lobe	357 (58.9)	62 (20.3)	28 (68.3)	3 (25.0)	0
Left lobe	65 (10.7)	194 (63.6)	8 (19.5)	8 (66.7)	2 (100.0)
Segmental	5 (0.8)	5 (1.6)	0	0	0
Unknown	0	3 (1.0)	0	0	0
Activity planned (GBq), median (range)	1.25 (0.32-3.00)[ix]	0.72 (0.20-2.00)[viii]	1.01 (0.38-1.81)[i]	0.77 (0.31-1.45)	0.84 (0.63-1.04)
Activity administered (GBq), median (range)	1.17 (0.11-2.29)[iv]	0.66 (0.10-1.81)[v]	0.95 (0.33-1.79)	0.71 (0.11-1.45)	0.81 (0.62-0.99)
Hospital stay duration (days), N (%)					
<24 hours	590 (97.8)	294 (98.0)	40 (97.6)	12 (100.0)	2 (100.0)
≥24 hours	13 (2.2)[iii]	6 (2.0)[v]	1 (2.4)	0	0
Total liver volume (mL), median (range)	1,751.5 (664.0-5,844.0)[xxii]	1,795.1 (842.0-4,528.0)[xix]	1,673.5 (922.0-4,304.3)[xi]	2,046.6 (1,279.5-2,664.1)[vi]	2,141.6 (2,139.4-2,143.8)
Treated liver volume (mL), median (range)	1,409 (226.0-4,771.6)[xxiv]	660 (116.0-3463)[xx]	735 (250.0-2,032.0)[xiv]	NA[x]	NA[ii]
Total tumor volume (mL), median (range)	139.5 (2.8-3,329.0)[xxiii]	80 (2.1-1978.0)[xxi]	105.65 (4.7-753.9)[xiii]	249.3 (3.6-500.3)[vi]	133.45 (18.0-248.9)
Tumor-to-treated-liver ratio (%), median (range)	15 (0.1-100)[xvii]	12 (0.1-95)[xvi]	15 (0.3-70)[v]	15 (0.3-65)[i]	6 (0.8-12)

Missing baseline data on: [i], 1 patient; [ii], 2 patients; [iii], 3 patients; [iv], 4 patients; [v], 5 patients; [vi], 6 patients; [vii], 7 patients; [viii], 10 patients; [ix], 11 patients; [x], 12 patients; [xi], 19 patients; [xii], 19 patients; [xiii], 23 patients; [xiv], 30 patients; [xv], 35 patients; [xvi], 40 patients; [xvii], 48 patients; [xviii], 50 patients; [xix], 122 patients; [xx], 160 patients; [xxi], 176 patients; [xxii], 206 patients; [xxiii], 274 patients; [xxiv], 281 patients; BSA, body surface area; NA, not available.

Table S5 Post-^{90}Y-RE chemotherapy history for advanced mCRC, stratified by the setting of ^{90}Y-RE relative to prior chemotherapy lines

Post-SIRT agents	^{90}Y-RE Setting relative to prior chemotherapy lines, N (%)				
	1st-line ^{90}Y-RE (N=35)	2nd-line ^{90}Y-RE (N=206)	3rd-line ^{90}Y-RE (N=184)	4th+ line ^{90}Y-RE (N=158)	Unknown (N=23)
Number of patients treated post-SIRT	3 (8.6)	15 (7.3)	13 (7.1)	12 (7.6)	0
Continuation of regimen used pre-SIRT	0	3 (1.5)	6 (3.3)	8 (5.1)	0
Fluoropyrimidine	2 (5.7)	10 (4.9)	6 (3.3)	8 (5.1)	0
Oxaliplatin	1 (2.9)	3 (1.5)	3 (1.6)	3 (1.6)	0
Irinotecan	0	9 (3.5)	9 (4.9)	3 (1.6)	0
Any biologic agent	0	12 (5.8)	9 (4.9)	9 (5.7)	0
Bevacizumab	0	11 (5.3)	4 (2.2)	2 (1.3)	0
EGFR inhibitor	0	6 (2.9)	7 (3.8)	9 (5.7)	0
Unspecified agent(s)	1 (2.9)	1 (0.5)	0	0	0

mCRC, metastatic colorectal cancer; SIRT, selective internal radiation therapy.

Table S6 Common (≥1% or recognized potential complications)* all-causality adverse events by severity (CTCAE v3) according to the interval from first ^{90}Y-RE procedure (day 0) in 606 patients

System organ, class	Day 0, N (%)			Days 1-7, N (%)			Days 8-90, N (%)			Days 91-184, N (%)		
	Unknown	CTCAE grade 1-2	CTCAE grade ≥3	Unknown	CTCAE grade 1-2	CTCAE grade ≥3	Unknown	CTCAE grade 1-2	CTCAE grade ≥3	Unknown	CTCAE grade 1-2	CTCAE grade ≥3
Gastrointestinal	0	50 (8.3)	7 (1.2)	1 (0.2)	140 (23.1)	17 (2.8)	2 (0.3)	152 (25.1)	39 (6.4)	3 (0.5)	32 (5.3)	10 (1.7)
Abdominal pain	0	30 (5.0)	6 (1.0)	1 (0.2)	96 (15.8)	10 (1.7)	2 (0.3)	114 (18.8)	22 (3.6)	0	23 (3.8)	5 (0.8)
Nausea	0	30 (5.0)	2 (0.3)	2 (0.3)	76 (12.5)	3 (0.5)	2 (0.3)	65 (10.7)	3 (0.5)	1 (0.2)	10 (1.7)	1 (0.2)
Vomiting	0	9 (1.5)	0	0	20 (3.3)	5 (0.8)	0	31 (5.1)	3 (0.5)	1 (0.2)	1 (0.2)	1 (0.2)
GI ulcer	0	0	0	0	1 (0.2)	0	0	6 (1.0)	7 (1.2)	1 (0.2)	4 (0.7)	3 (0.5)
Abdominal distension	0	0	0	0	0	1 (0.2)	0	14 (2.3)	1 (0.2)	0	2 (0.3)	0
Dyspepsia	0	0	0	0	5 (0.8)	0	0	12 (2.0)	0	0	4 (0.7)	0
Gastritis	0	0	0	0	0	1 (0.2)	0	3 (0.5)	1 (0.2)	0	0	1 (0.2)
Duodenitis	0	0	0	0	0	0	0	0	1 (0.2)	0	1 (0.2)	0
Intestinal obstruction	0	0	0	0	1 (0.2)	1 (0.2)	0	0	3 (0.5)	1 (0.2)	1 (0.2)	0
Constipation	0	0	0	0	11 (1.8)	0	2 (0.3)	8 (1.3)	0	0	0	0
Diarrhea	0	0	0	0	5 (0.8)	0	0	4 (0.7)	0	0	0	0
Flatulence	0	2 (0.3)	0	0	1 (0.2)	0	0	4 (0.7)	0	0	0	0
Constitutional	0	32 (5.3)	5 (0.8)	3 (0.5)	114 (18.8)	7 (1.2)	6 (1.0)	162 (26.7)	25 (4.1)	4 (0.7)	25 (4.1)	6 (1.0)
Fatigue	0	28 (4.6)	4 (0.7)	0	96 (15.8)	6 (1.0)	4 (0.7)	154 (25.4)	22 (3.6)	2 (0.3)	21 (3.5)	4 (0.7)
Fever	0	3 (0.5)	1 (0.2)	2 (0.3)	28 (4.6)	0	1 (0.2)	18 (3.0)	1 (0.2)	0	2 (0.3)	0
Weight loss	0	0	0	0	1 (0.2)	0	1 (0.2)	6 (1.0)	0	0	4 (0.7)	0
Peripheral edema	0	0	0	0	0	0	1 (0.2)	1 (0.2)	2 (0.3)	2 (0.3)	2 (0.3)	2 (0.3)
Psychiatric	0	2 (0.3)	0	1 (0.2)	18 (3.0)	3 (0.5)	3 (0.5)	26 (4.3)	3 (0.5)	0	3 (0.5)	0
Anorexia nervosa	0	2 (0.3)	0	1 (0.2)	17 (2.8)	3 (0.5)	3 (0.5)	26 (4.3)	3 (0.5)	0	3 (0.5)	0
Hepatobiliary	0	0	0	0	5 (0.8)	0	0	43 (7.1)	35 (5.8)	2 (0.3)	31 (5.1)	22 (3.6)
Hyperbilirubinemia	0	0	0	0	1 (0.2)	0	0	36 (5.9)	18 (3.0)	1 (0.2)	30 (5.0)	18 (3.0)
Ascites	0	0	0	0	0	0	1 (0.2)	9 (1.5)	11 (1.8)	1 (0.2)	3 (0.5)	6 (1.0)
REILD	0	0	0	0	0	0	5 (0.8)	2 (0.3)	3 (0.5)	1 (0.2)	1 (0.2)	0
Cholecystitis	0	0	0	0	2 (0.3)	0	0	3 (0.5)	1 (0.2)	0	1 (0.2)	1 (0.2)
Hepatic failure	0	0	0	0	1 (0.2)	0	0	2 (0.3)	2 (0.3)	2 (0.3)	0	0
Musculoskeletal	0	2 (0.3)	1 (0.2)	0	7 (1.2)	0	1 (0.2)	8 (1.3)	0	0	2 (0.3)	0
Back pain	0	0	0	0	5 (0.8)	0	0	1 (0.2)	0	0	2 (0.3)	0
Vascular disorders	0	1 (0.2)	0	0	3 (0.5)	3 (0.5)	1 (0.2)	4 (0.7)	3 (0.5)	1 (0.2)	0	1 (0.2)
Respiratory	0	1 (0.2)	0	1 (0.2)	8 (1.3)	1 (0.2)	1 (0.2)	9 (1.5)	1 (0.2)	0	3 (0.5)	0
Influenza	0	1 (0.2)	0	0	6 (1.0)	0	1 (0.2)	4 (0.7)	0	0	0	0

*, at all time-points. This table reports the highest grade of adverse event reported by each patient within each time interval. GI, gastrointestinal; REILD, radioembolization-induced liver disease.

Table S7 All-causality changes in laboratory values at baseline and change from baseline at day 30 and 90 with corresponding percentage with severe events (all CTCAE grades 3 and 4)

Events	Baseline				Day 30*				Day 90*			
	N	Median (range)	% patients		N	Median change from baseline (range)	% patients		N	Median change from baseline (range)	% patients	
			Grade 3	Grade 4			Grade 3	Grade 4			Grade 3	Grade 4
Total bilirubin	593	0.6 (0.1-18.3)	0.2	0.2	144	0.1 (–1.0-12.8)	1.8	0.6	225	0.1 (–1.4-33.1)	4.9	2.7
Albumin	591	3.7 (1.6-4.8)	1.4	0	163	–0.2 (–1.4-1.2)	1.8	0	218	–0.3 (–2.3-1.1)	4.1	0
Alkaline phosphatase	592	146.0 (24.0-1,565.0)	3.0	0	166	23.0 (–274.0-407.0)	2.3	0	228	62.0 (–342.0-1,209.0)	7.8	0
Aspartate aminotransferase	590	35.0 (10.0-353.0)	1.5	0	161	4.0 (–62.0-428.0)	4.2	0	225	12.0 (–172.0-544.0)	2.2	0

*, based on last laboratory test within previous 30-day time interval.

Table S8 Kaplan-Meier analysis and univariate Cox proportional hazards model of survival by baseline characteristics

Characteristic	Survival, months[†]				Univariate Cox proportional hazards model		
	N	Median	95% CI	P value	Hazard ratio	95% CI	P value between sub-groups
All	606	9.6	9.0-11.1	na			
Gender				0.473	0.94	0.78-1.12	0.474
Female	233	9.4	8.7-11.4				
Male	373	10.0	8.9-11.8				
Race				0.855	1.02	0.85-1.22	0.854
Caucasian	398	9.5	8.9-11.2				
Non-Caucasian	208	9.6	8.5-12.2				
Age				0.335	1	1.00-1.01	0.387
<70 years	446	9.7	9.0-11.4				
≥70 years	160	9.3	8.0-12.1				
ECOG performance status				0.009[i]	1.35	1.09-1.67	0.005[i]
0	168	11.2	9.1-13.1				
1	72	8.1	6.4-11.0				
2	14	6.0	2.3-12.2				
3	3	5.0	1.3-11.0				
Extra-hepatic metastases				<0.001	1.73	1.45-2.08	<0.001
No	393	12.1	10.8-13.6				
Yes	213	7.4	6.1-8.5				
In-situ primary				0.016	1.37	1.06-1.77	0.017
No	522	10.0	9.1-11.8				
Yes	78	8.1	6.2-10.4				
Metastases				0.055	0.821	0.67-1.00	0.055
Metachronous	173	11.2	9.0-13.1				
Synchronous	396	9.3	8.5-10.6				
Ascites				<0.001[ii]	2.65	1.72-4.09	<0.001[ii]
No	563	10.0	9.2-11.8				
Yes (controlled)	5	2.4	0.7-22.9				
Yes (uncontrolled)	23	5.5	3.6-7.4				
Prior liver surgery/ablation				0.067	0.83	0.68-1.01	0.067
No	438	9.4	8.5-11.0				
Yes	168	10.4	8.9-13.1				
Prior non-surgical liver-directed procedure				0.44	1.16	0.80-1.68	0.439
No	569	9.6	9.0-11.2				
Yes	37	9.9	6.5-13.9				
Prior lines of chemotherapy				<0.001	1.22	1.13-1.31	<0.001
RE 2nd-line	206	13.0	10.5-14.6				
RE 3rd-line	184	9.0	7.8-11.0				
RE 4th-line +	158	8.1	6.4-9.3				
RE 1st-line				0.041			
All	35	13.5	7.2-17.1	NA			
<75 years	17	25.2	9.3-36.5				
≥75 years	18	11.9	4.0-15.6				

Table S8 (*continued*)

Table S8 (*continued*)

Characteristic	Survival, months[†]				Univariate Cox proportional hazards model		
	N	Median	95% CI	P value	Hazard ratio	95% CI	P value between sub-groups
Number of ^{90}Y-RE procedures				0.005[iii]	0.84	0.75-0.95	0.006[iii]
1	301	8.9	7.7-10.8				
2	264	9.6	8.6-11.2				
3	29	17.7	11.2-23.7				
4	10	19.0	9.3-25.4				
5	2	28.1	26.4-29.8				
1st to 2nd ^{90}Y-RE procedure >90 days				<0.001	2.4	1.74-3.31	<0.001
No	58	18.3	15.8-23.1				
Yes	246	9.2	8.1-9.9				
Tumor-to-target liver involvement				<0.001	11.5	6.98-18.93	<0.001
<25%	388	12.8	10.8-13.6				
25-50%	148	6.5	5.7-8.1				
>50%	22	6.0	3.6-9.1				
Carcinoembryonic antigen				<0.001	1	1.00-1.00	<0.001
< median	215	13.6	12.2-16.3				
≥ median	215	7.4	6.6-8.5				
Total bilirubin, CTC grade				<0.001	1.43	1.31-1.56	<0.001
0	556	10.4	9.3-11.9				
≥1	37	3.8	2.5-7.4				
Albumin, CTC grade				<0.001	0.42	0.36-0.50	<0.001
0	392	13.0	11.6-13.9				
≥1	199	6.3	5.4-7.1				
Alkaline phosphatase, CTC grade				<0.001	1	1.00-1.00	<0.001
0	241	15.7	13.9-17.7				
≥1	351	7.1	6.3-8.1				
Alanine transaminase, CTC grade				0.117	1	1.00-1.00	0.009
0	409	10.8	9.0-12.2				
≥1	175	9.1	8.2-9.9				
Aspartate aminotransferase, CTC grade				<0.001	1	1.00-1.00	0.009
0	296	13.9	12.2-15.6				
≥1	294	7.2	6.3-8.7				
Creatinine, CTC grade				0.041	1.2	0.90-1.59	0.210
0	569	9.6	9.0-11.2				
≥1	26	7.1	4.7-12.2				
Hemoglobin, CTC grade				<0.001	0.86	0.82-0.90	<0.001
0	356	12.2	10.6-13.6				
≥1	238	7.6	6.4-9.0				
White blood cell count, CTC grade				0.499	1.05	1.02-1.07	<0.001
0	553	9.4	8.9-11.0				
≥1	41	12.1	9.3-13.3				

P value for continuous variables by one-way ANOVA, P values for dichotomous variables by Fisher's exact test, and P value for nominal categorical variables by Chi-Square general association. [†], median survival calculated by Kaplan-Meier analysis; [i], P value: ECOG ps 0 *vs*. 1 *vs*. 2-3; [ii], P value: ascites (not controlled) *vs*. ascites (controlled) or none; [iii], P value: RE procedures 1 *vs*. 2 *vs*. 3-5; CI, confidence interval; NA, not applicable; HR, hazard ratio.

Table S9 Multivariate analysis of significant single-vector prognostic indicators[†]

Variable	Hazard ratio (95% CI)	P value
All patients (N=606)		
Tumor-to-target-liver ratio (%)	3.36 (1.76-6.39)	<0.001
Extra-hepatic metastases	1.51 (1.22-1.86)	<0.001
Albumin (mg/dL)	0.65 (0.53-0.80)	<0.001
Aspartate aminotransferase (U/L)	1.01 (1.00-1.01)	<0.001
Alkaline phosphatase (U/L)	1.00 (1.00-1.00)	<0.001
White blood cell count	1.03 (1.00-1.06)	0.024
Number of lines of prior chemotherapy	1.10 (1.01-1.91)	0.029
Ascites (not controlled) vs. ascites (controlled) or none	1.63 (1.00-2.65)	0.049
Sub-set with known ECOG performance status (N=257)		
Number of lines of prior chemotherapy	1.28 (1.12-1.45)	<0.001
Albumin (mg/dL)	0.62 (0.46-0.84)	0.002
EHD	1.57 (1.16-2.13)	0.004
Prior lines of chemotherapy	1.28 (1.12-1.45)	<0.001
Aspartate aminotransferase (U/L)	1.01 (1.00-1.01)	0.003
Albumin (mg/dL)	0.62 (0.46-0.84)	0.002
Alkaline phosphatase (U/L)	1.00 (1.00-1.00)	0.010
Creatinine (mg/dL)	1.76 (1.09-2.84)	0.022
Hemoglobin (g/dL)	0.92 (0.84-1.00)	0.038

[†], model selection is by best subsets approach using input variables that are statistically significant in the univariate Kaplan-Meier estimates and Cox proportional hazards model (P<0.05). Statistically significant variables by univariate Kaplan-Meier or Cox proportional hazards models were candidate variables for the multivariate model.