

Factors Affecting Oncologic Outcomes of 90Y Radioembolization of Heavily Pre-Treated Patients With Colon Cancer Liver Metastases

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Abstract

One-year overall survival prediction nomogram included 6 easy-to-obtain pre Yttrium-90 radioembolization parameters and provided good prediction of overall survival post Yttrium-90 radioembolization. This can be useful for pretreatment patient stratification and counseling of heavily pretreated patients with colorectal cancer liver metastases. Baseline maximum standardized uptake value predicted liver progression-free survival.

Introduction: The purpose of this study was to identify predictors of overall (OS) and liver progression-free survival (LPFS) following Yttrium-90 radioembolization (RAE) of heavily pretreated patients with colorectal cancer liver metastases (CLM), as well as to create and validate a predictive nomogram for OS. **Materials and Methods:** Metabolic, anatomic, laboratory, pathologic, genetic, primary disease, and procedure-related factors, as well as pre- and post-RAE therapies in 103 patients with CLM treated with RAE from September 15, 2009 to March 21, 2017 were analyzed. LPFS was defined by Response Evaluation Criteria In Solid Tumors 1.1 and European Organization for Research and Treatment of Cancer criteria. Prognosticators of OS and LPFS were selected using univariate Cox regression, adjusted for clustering and competing risk analysis (for LPFS), and subsequently tested in multivariate analysis (MVA). The nomogram was built using R statistical software and internally validated using bootstrap resampling. **Results:** Patients received RAE at a median of 30.9 months (range, 3.4-161.7 months) after detection of CLM. The median OS and LPFS were 11.3 months (95% confidence interval, 7.9-15.1 months) and 4 months (95% confidence interval, 3.3-4.8 months), respectively. Of the 40 parameters tested, 6 were independently associated with OS in MVA. These baseline parameters included number of extrahepatic disease sites ($P < .001$), carcinoembryonic antigen ($P < .001$), albumin ($P = .005$), alanine aminotransferase level ($P < .001$), tumor differentiation level ($P < .001$), and the sum of the 2 largest tumor diameters ($P < .001$). The 1-year OS of patients with total points of < 25 versus > 80 was 90% and 10%, respectively. Bootstrap resampling showed good discrimination (optimism corrected c-index = 0.745) and calibration (mean absolute prediction error = 0.299) of the nomogram. Only baseline maximum standardized uptake value was significant in MVA for LPFS prediction ($P < .001$; SHR = 1.06). **Conclusion:** The developed nomogram included 6 pre-RAE parameters and provided good prediction of survival post-RAE in heavily pretreated patients. Baseline maximum standardized uptake value was the single significant predictor of LPFS.

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Introduction

Yttrium-90 (90Y) radioembolization (RAE) is an United States Food and Drug Administration-approved liver brachytherapy, recommended through the National Comprehensive Cancer Network (NCCN) and the European Society for Medical Oncology (ESMO) guidelines for the treatment of colorectal cancer liver metastases (CLM) in the salvage setting with liver disease progression while on or after second-line chemotherapy with encouraging oncologic outcomes.¹⁻¹⁸

RAE performed at this advanced stage of a terminal disease has the goal of prolonging patient survival with limited if any impact on quality of life. Currently, a decision for RAE is recommended through a multidisciplinary discussion.⁷ In clinical practice, recommendations for patients with refractory disease are challenging, because this population often presents with advanced tumor load, unfavorable biologic tumor characteristics, comorbidities, or poor performance status. It is thus not surprising that the range of reported outcomes post-RAE is highly variable. Objective response rates (ORRs) varied between 10% and 48% when RAE was applied in the third and subsequent chemotherapy regiment settings.^{10,17,19,20} Thus, careful patient selection is extremely important to minimize the risk of treatment-related complications and unnecessary hospitalization. Current exclusion criteria do not always provide adequate risk stratification or an optimal estimation of patient survival. Poor outcome may be a consequence of more extensive disease, but may also be associated with RAE-induced adverse events. A predictive scoring system can aid a rational decision with estimation of each patient's risk/benefit ratio prior to undergoing RAE.

The aim of this study was to analyze metabolic, anatomic, laboratory, pathologic, primary disease-related and genetic biomarkers, and procedure-related factors as well as pre- and post-RAE therapies that can be associated with liver progression-free survival (LPFS) and overall survival (OS). In addition, our goal was to create and internally validate a predictive survival nomogram using pre-RAE patient characteristics.

Materials and Methods

Ethical Considerations and Patient Selection

Institutional Review Board waiver of approval was obtained for this retrospective review of our prospectively created and maintained Health Insurance Portability and Accountability Act of 1996 (HIPAA)-registered and compliant colorectal cancer liver metastases (CLM) RAE database. All patients with CLM treated with 90Y RAE from September 15, 2009 to March 21, 2017 were included.

Inclusion and Exclusion Criteria

All patients treated with RAE were eligible for inclusion in the study.

Eligibility criteria for RAE in our practice included: age \geq 18 years; Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2; histologically confirmed primary adenocarcinoma of the colon or rectum; CLM considered unresectable or not amenable to percutaneous ablation; adequate blood cell counts (white blood cell count $> 1.5 \times 10^9/L$, platelet count $> 50 \times 10^9/L$); adequate renal function (creatinine < 1.5 mg/dL), and total bilirubin level ≤ 1.5 mg/dL.

Exclusion criteria were: prior hepatic radiotherapy; severe cirrhosis; severe portal hypertension; uncorrectable flow to the gastrointestinal tract and/or $> 20\%$ shunting to the lungs, as determined by technetium-99m labeled macroaggregated albumin (99mTc-MAA) hepatic arterial perfusion scintigram (mapping). All patients at the time of RAE had liver-dominant disease and were considered candidates for RAE even in the face of oligometastatic (up to 5 sites) extrahepatic disease that was stable or controlled by chemotherapy.

Preprocedural Workup and Angiographic Mapping

All patients were evaluated at a clinic visit within 30 days before RAE. Past medical history was reviewed, physical examination was performed, and relevant baseline laboratory values were evaluated. Preprocedural baseline imaging with liver dynamic (ideally triphasic) computed tomography (CT) and 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT was available within 30 days from RAE for accurate restaging of disease and for calculation of liver and CLM volumes for 90Y dosimetry.

All patients underwent angiographic evaluation and 99mTc-MAA mapping prior to RAE. During arteriography, hepatic arterial anatomy and tumor vascular supply were assessed. Extrahepatic vessels with hepatofugal flow within 3 cm from the desired point of 90Y administration were prophylactically coil-embolized to prevent inadvertent delivery of 90Y in extrahepatic sites. Once the desired location(s) of RAE administration(s) was determined, a total of 4 to 5 mCi of 99mTc-MAA were injected at desired sites of 90Y arterial infusion, and subsequent planar scintigraphy and SPECT/CT imaging were performed to calculate the lung shunt fraction and to detect extrahepatic activity.¹⁷

RAE Procedure

Approximately 2 weeks after mapping angiography, patients underwent RAE with SIR-Spheres (Sirtex Medical, Sydney, Australia) or glass microspheres (Therasphere; MDS Nordion, Ottawa, Ontario, Canada). Glass-based microspheres were introduced in March 2015 and were specifically used instead of SIR-spheres in patients with higher risk of developing stasis: in the presence of constricted or small caliber arteries as well as in patients with history of prior nonanatomic liver resections or intra-arterial hepatic infusion pump chemotherapy, who presented with tortuous or constricted vessels at mapping.

As of April 2013, 90Y resin microspheres were administered using undiluted contrast medium, which allowed real-time infusion monitoring and resulted in shorter infusion time and reduced fluoroscopy radiation dose, as previously described.¹⁸

The total activity of 90Y resin microsphere (in GBq) for each patient was calculated using body surface area (BSA) method with the following formula:²¹

$$\text{SIR-spheres Activity} = (\text{treatment liver volume} / \text{total liver volume}) * \\ [(\text{BSA} - 0.2) + (\text{fraction of liver with tumor})]$$

For 90Y glass microspheres, the total activity of 90Y was calculated using the following formula:^{7,22}

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$$\text{Therasphere activity (GBq)} = \text{Desired dose (Gy)} \times \text{Mass of selected live target lobe}/50$$

In cases where lung shunting was between 10% and 15%, patients received a 20% reduction of the calculated radiation dose. Adjustments were not made based on prior treatment history.

CLMs confined to 1 lobe were treated in 1 session, whereas bilobar disease was treated in 2 sessions separated by 4 to 8 weeks. If the limited extent of disease permitted sublobar microsphere infusions, the patients with bilobar disease were also treated within 1 session (as long as not more than 50% of liver parenchyma was exposed to the radiation at each session). Patients with a single hepatic lobe postresection were treated in lobar or sublobar fashion, depending on the extent and location of disease. In general, we aimed to treat as selectively as possible to treat all tumors while sparing uninvolved liver parenchyma.

Study Objectives

Primary objectives included: (1) Analysis of LPFS and factors associated with LPFS; LPFS was defined as the time between the treatment date until disease progression or death/last follow-up. It was calculated using competing risk analysis. If there was no liver disease progression and no imaging available within 6 months before death, then the date of last imaging was included in competing risk analysis. If there was no liver disease progression and there was imaging within 6 months before death available, death date was included in the competing risk analysis. LPFS was evaluated using European Organisation for Research and Treatment of Cancer (EORTC) and Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria, depending on imaging availability. In cases of differing responses between the criteria, the concordance between both modalities imaging findings was used to determine LPFS. (2) Overall survival (OS) and factors associated with it; OS was defined as the time from initial RAE to patient death or last follow-up.

Secondary objectives included: (1) Evaluation of local tumor response and ORR; (2) Assessment of radiologic response within the treated hepatic territory.

Imaging was performed using contrast-enhanced CT and 18F-FDG PET/CT at 4 to 8 and 12 to 16 weeks post-RAE and compared with the pre-RAE scans. Scans at 4 to 8 weeks were used as the new baseline for subsequent imaging obtained every 2 to 4 months thereafter. Radiologic response in the liver was assessed by changes in size and metabolic activity using RECIST 1.1 and EORTC criteria. Using EORTC criteria, 25% threshold was chosen to define response or disease progression, using the sum of up to 5 liver lesions maximum standard uptake values (SUVmax). In patients with 2 RAE sessions, response was evaluated for each treated region. ORR was defined as the percentage of patients with partial or complete response within 12 to 16 weeks post-RAE, based on RECIST 1.1 and EORTC criteria.

Prognosticators of LPFS and OS

A total of 24 factors were analyzed as potential prognosticators of LPFS. They included primary disease-related variables, liver tumor burden, carcinoembryonic antigen (CEA) level, genetic mutations (KRAS, BRAF, PI3KCA), prior and post-RAE systemic regimens for metastatic colorectal cancer, procedure-related parameters (sphere type, delivered radiation dose, and occurrence of stasis), pre-RAE laboratory parameters (neutrophil/lymphocyte ratio [NLR] and platelet/lymphocyte ratio [PLR]), and metabolic tumor uptake parameters (SUVmax, SUVpeak, SUVmean, metabolic tumor volume [MTV], and total lesion glycolysis [TLG]) of the most metabolically active tumor.

Forty factors were analyzed as potential prognosticators of OS. In addition to the factors described above, we included the following factors to overall survival analysis: patients' age, pre-RAE liver function laboratory parameters, primary disease-related variables, CEA level, pre-and post-RAE therapies, post-RAE NLR and PLR, disease-free survival, time from liver metastases diagnosis to RAE, LPFS, and number of extrahepatic disease sites.

Statistical Analysis

The median follow-up period was calculated for the patients who were alive on last follow-up. Prognosticators of OS and LPFS were selected using univariate Cox regression, adjusted for clustering and competing risk analysis (for LPFS) and subsequently tested in multivariate analysis (MVA). Only pretreatment easy-to-obtain and well-established parameters were included into MVA as potential predictors of OS. All the nomogram factors were included as continuous variables (except for tumor differentiation level) for more accurate estimation of each factor's predictive value. LPFS association with OS was assessed using Cox regression analysis, including only the patients who had liver disease progression.

The nomogram was built using R statistical software and internally validated using bootstrap resampling. Statistical analysis was performed using STATA 12.1 software. A *P*-value < .05 was considered significant.

Results

Study Population

A total of 103 patients treated with 136 RAE sessions were included in the study. The median follow-up time was 9.02 months (range, 0.7-42.7 months). Sixty-three (61%) of 103 patients were men and 40 (39%) were women, with a median age of 60 years (range, 24-87 years). Seventy-six (74%) of 103 patients had synchronous liver metastases. The median time from diagnosis of CLM to RAE was 30.9 months (range, 3.4-161.7 months).

Eighty-one (79%) of 103 patients were treated with resin microspheres, 21 (20%) of 103 with glass microspheres, 1 (1%) of 103 with both (initially with resin and local tumor progression (LTP) retreatment with glass microspheres almost 3 years later). Seventy-three (71%) of 103 patients were treated in 1 RAE session and 26 (25%) of 103 in 2 sessions. Seven (7%) of 103 patients underwent repeat RAE for: (1) LTP in previously treated region (in 3 patients); (2) progression of disease in untreated liver lobe (in 3 patients); (3) additional RAE in the same region owing to poor

Table 1 Patient Demographics and Disease Characteristics

Patient Demographics and Disease Characteristics	No. Patients
Median age, y (range)	60 (24-87)
Gender	
Male	63
Female	40
Synchronous liver disease	
Yes	81
No	22
Pathologic evidence of vascular invasion from primary tumor	
Yes	44
No	33
Unknown	26
KRAS mutation	
Yes	29
No	58
Unknown	16
PIK3CA mutation	
Yes	10
No	41
Unknown	52
Surgical resection of primary disease	
Yes	82
No	20
Unknown	1
Median CEA level before RAE, ng/mL (range)	55.3 (1.1-23,937.6)
Time from diagnosis of CRC to diagnosis of CLM	
Mean, mos	6.3
Median, mos (range)	0 (0-64.2)
Median time from diagnosis of CLM to RAE, mos (range)	30.9 (3.4-161.7)
Type of microspheres	
Resin	81
Glass	21
Both	1
Prior liver surgery	
Yes	49
No	54
Prior HAIP chemotherapy	
Yes	53
No	50
Prior systematic chemotherapy	
≥ 3 lines	30
< 3 lines	73
Prior bevacizumab	
Yes	63
No	40
Extent of hepatic replacement by tumor at time of RAE	
< 25%	89
≥ 25%	14

Table 1 Continued

Patient Demographics and Disease Characteristics	No. Patients
Presence of extrahepatic disease at time of RAE	
Yes	74
No	29
No. confirmed metastatic extrahepatic organ systems at time of RAE	
0	29
1	38
2	24
3	9
4	3
ECOG status at time of RAE	
0	33
1	26
2	2
Unknown	42
Distribution of hepatic disease at time of RAE	
Unilobar	17
Unilobar with 1 hepatic lobe left	11
Bilobar	75
Incidence of stasis in resin microspheres infusions	39/146 (27%)
Prescribed radiation dose delivered to tumor per procedure, % (range)	96 (19-106)
No. RAE sessions per patient	
1	73
2	30
Post-RAE HAIP therapy	
Yes	18
No	85
No. post-RAE systemic chemotherapy lines	
0	25
1	39
2	22
3	15
4	1
Unknown	1
Post-RAE ablation	
Yes	5
No	98

Abbreviations: CEA = Carcinoembryonic antigen level; CLM = colorectal liver metastases; CRC = colorectal cancer; HAIP = hepatic arterial infusion pump therapy; RAE = radioembolization.

tumor coverage during initial RAE (in 1 patient; partial recanalization of embolized vessel precluded flow redirection to a tumor region during initial RAE). Patient characteristics are described in [Table 1](#).

Local Tumor Response, ORR and LPFS

On the first imaging post-RAE at 4 to 8 weeks, 39% of patients had partial response according to EORTC criteria, whereas 59% had stable disease according to RECIST 1.1. ORR (complete or

Table 2 Local Tumor Response on First Imaging After RAE (at 4 to 8 Weeks) and at Second Follow-up (at 12 to 16 Weeks)

Response	At 4 to 8 Weeks, n (%)		At 12 to 16 Weeks, n (%)	
	EORTC	RECIST 1.1	EORTC	RECIST 1.1
CR	5/84 (6)	1/94 (1)	3/55 (5)	0
PR	33/84 (39)	0	9/55 (16)	3/76 (4)
SD	17/84 (20)	55/94 (59)	7/55 (13)	39/76 (51)
POD	20/84 (24)	25/94 (27)	35/55 (64)	31/76 (41)
Different response in treatment regions				
SD + PR	4/84 (5)	3/94 (3)	—	—
SD + POD	2/84 (2)	9/94 (9)	—	3/76 (4)
PR + POD	2/84(2)	1/94 (1)	—	—
SD + CR	1/84 (1)	0	—	—
CR + POD	—	—	1/55 (2)	—
Not applicable (absent follow-up or baseline imaging, measurements could not be obtained owing to technical problems)	19/103 (18)	9/103 (9)	48/103 (47)	27/103(26)

Abbreviations: CR = Complete response; LTP = local tumor progression; POD = progression of disease; PR = partial response; SD = stable disease.

partial response) at 12 to 16 weeks post-RAE was 44 (52%) of 84 by EORTC and 6 (6%) of 94 by RECIST 1.1 criteria. Local tumor response at initial 4 to 8 weeks post-RAE imaging is described in Table 2.

Despite the lack of statistical significance, the patients who developed early/late stasis in at least 1 infusion during 90Y RAE had roughly double the risk for LTP on initial scan, defined by RECIST 1.1 (odds ratio [OR], 1.81; $P = .19$) or EORTC criteria (OR, 2.2; $P = .14$).

Despite the lack of statistical significance, the patients who had $\geq 96\%$ of prescribed radiation dose delivered had a 44% lower risk of LTP at first imaging, compared with patients who received $< 96\%$ of the dose, when LTP was defined by EORTC criteria (OR, 0.56; $P = .32$).

Sphere type was neither associated with LTP on first follow-up, evaluated by RECIST 1.1 or EORTC criteria ($P = .99$ for both), nor with LPFS (SHR = 1.08; $P = .77$).

LPFS and Its Prognosticators

The median LPFS was 4 months (95% CI, 3.4-4.9 months). Six-month and 1-year LPFS were 27% (95% CI, 18%-36%) and 9% (95% CI, 3%-16%).

Only increased metabolic tumor parameters (SUVmax, SUVpeak, MTV, and TLG) and decreased time from CLM diagnosis to RAE were significantly associated with decreased LPFS on univariate analysis (Table 3). Owing to correlation between metabolic parameters, only 2 variables (SUVmax and time from CLM diagnosis to RAE) were included in the multivariate analysis (MV). Only SUVmax was a significant predictor of LPFS on MV analysis (HR, 1.06; 95% CI, 1.02-1.1; $P = .003$).

OS

The median OS was 11.3 months (95% CI, 7.9-15.1 months). Six-month and 1-, 2-, and 3-year OS was 75% (95% CI, 64%-81%), 46% (95% CI, 35%-55%), 18% (95% CI, 11%-27%), and 15% (95% CI, 8%-24%), respectively. There were no deaths within 30 days post-RAE.

A total of 11 (11%) of 103 patients died within 3 months post-RAE. None of these deaths were considered directly or solely related to the RAE: 7 (64%) of 11 patients had evidence of liver disease progression; 8 (73%) of 11 patients also developed conditions that resulted in significant morbidity and were at least partially related to RAE, but did not lead to subsequent death. Analysis of deaths within 3 months post-RAE is presented in Table 4.

Factors Associated With OS: Creation of Predictive Nomogram

Twenty-one of 40 factors were associated with OS post-RAE in univariate analysis (Table 3). Considering the number of deaths during the study period (87 of 103; 84%), only 8 factors with low correlation between each other could be included in MV analysis.

Six of 8 pre-RAE parameters included in the MV analysis were significantly associated with OS and were subsequently used to build an OS prediction nomogram (Table 5). These factors included: (1) baseline CEA level; (2) baseline alanine transaminase (ALT) level; (3) albumin level; (4) the sum of the sizes of the 2 largest CLM diameters in the treatment region; (5) the number of extrahepatic disease sites; and (6) tumor differentiation level (Figure 1).

One patient had CEA level $> 20,000$ ng/mL and was considered as an outlier in our study that contributed to very high CEA values in the nomogram. It was excluded from internal validation as it was adversely affecting the model fit and evaluation.

Each MV analysis factor was assigned points relative to each HR. The nomogram assigned the probability of 1-year survival by summing the point-scale scores for each variable. The total score projected on the bottom scale indicated the probability of 1-year survival. One-year OS of patients with total points < 25 indicated a 90% chance of 1-year survival, whereas a total sum of points of > 80 indicated an estimated 10% chance of 1-year survival. Bootstrap resampling showed good discrimination (optimism corrected c-index = 0.745) and calibration (mean absolute prediction error = 0.299) of the nomogram.

Table 3 Univariate Analysis for Prognosticators of OS and LPFS Post-RAE

No.	Variable Group	Variable	OS, P Value	HR	LPFS, P Value	SHR
1	Patient variable	Age	.23	0.76	—	—
2	Time variable	Time from diagnosis of CLM to RAE	.06	0.99	.034 ^a	0.99
3		Disease-free interval (from primary Rx to CLM)	.07	0.99	—	—
4	Primary disease- related variables	Primary tumor resection (no/yes)	.52	0.82	—	—
5		Nodal status of the primary (positive/negative)	.77	0.33	—	—
6		Lymphovascular invasion of primary (yes/no)	.03 ^a	1.74	.35	0.79
7		Tumor differentiation level (good/moderate vs. poor)	.009 ^a	2.05	.55	0.81
8		Synchronous versus metachronous liver metastases	.24	1.31	.31	1.27
9		Side of primary (left vs. right; transverse excluded)	.33	0.77	.45	1.25
10	Disease-related variables at time of RAE	Liver tumor burden ($\geq 25\%$ vs. $< 25\%$)	.056	1.77	.74	1.12
11		Number of EHD sites (range, 0-4)	.03 ^a	1.26	—	—
12		Sum of largest diameters of 2 liver lesions, cm	.001 ^a	1.08	.95	1
13		CEA level at time of RAE, ng/mL	$<.001^a$	1.0001	.07	1.0005
14	Genetic mutations	KRAS (positive/negative)	.16	1.45	.15	1.48
15		PI3KCA (positive/negative)	.78	1.13	.69	0.79
16		BRAF (positive/negative)	.88	0.89	.2	1.38
17	Prior to RAE variables	Prior hepatic artery infusion pump (no/yes)	.76	0.88	.71	0.92
18		Prior systemic therapy (≥ 3 lines vs. < 3 lines)	.84	1.05	.55	0.87
19		Prior liver surgery	.36	0.82	.75	0.93
20	RAE-related variables	% of prescribed radiation dose delivered	.43	1.004	.6	1.003
21		Sphere type (resin vs. glass microspheres)	.77	0.92	.87	0.95
22		Occurrence of stasis (yes/no)	—	—	.73	0.93
23	Metabolic tumor uptake parameters (of 1-5 most FDG-avid lesions)	SUV max (continuous)	.028 ^a	1.05	$<.001^a$	1.06
24		SUV peak (continuous)	.025 ^a	1.06	.001 ^a	1.08
25		SUV mean (continuous)	.004 ^a	1.13	.41	1.03
26		MTV (continuous)	$<.001^a$	1.001	$<.001^a$	1.0007
27		TLG (continuous)	$<.001^a$	1.0002	.046 ^a	1.0001
28	Pre-RAE laboratory parameters	Pre-RAE neutrophil/lymphocyte ratio	.02 ^a	1.05	.4	1.02
29		Pre-RAE platelet/lymphocyte ratio	.001 ^a	1.002	.12	1.001
30		Albumin	$<.001^a$	0.36	—	—
31		Total bilirubin	.4	1.26	—	—
32		Aspartate aminotransferase	$<.001^a$	1.02	—	—
33		Alanine aminotransferase	.003 ^a	1.01	—	—
34		Alkaline phosphatase	.001 ^a	1.002	—	—
35	Post-RAE laboratory parameters/therapies	Post-RAE neutrophil/lymphocyte ratio	.077	1.04	—	—
36		Post-RAE platelet/lymphocyte ratio	.6	1.0003	—	—
37		Post-RAE hepatic artery infusion pump	.001 ^a	0.42	—	—
38		Post-RAE ablation	.029 ^a	0.35	—	—
39		Post-RAE chemotherapy lines (≤ 1 vs. 2-4)	$<.001^a$	0.48	—	—
40		Post-RAE bevacizumab	.001 ^a	0.48	—	—
41		Liver progression-free survival, mos	.002 ^a	0.9	—	—

Abbreviations: CEA = Carcinoembryonic antigen level; CLM = colorectal liver metastases; EHD = extrahepatic disease; HR = hazard ratio; LPFS = liver progression-free survival; MTV = metabolic tumor volume; OS = overall survival; RAE = radioembolization; Rx = resection; SHR = sub-hazard ratio, SUV = standardized uptake value, TLG = total lesion glycolysis.

^aStatistically significant factors. Analyzed using Cox regression adjusted for clustering: 3 patients had 2 initial RAE treatments, thus were clustered.

Complications

The incidence of grade 1 to 2 toxicities was 44 (43%) of 102 patients (Table 6). The incidence of grade 3 to 4 toxicities was 14 (14%) of 102 patients (Table 6). Two patients in our study developed hepatic venous occlusion post-RAE: Budd-Chiari syndrome in 1 patient and right hepatic vein, inferior vena cava

thrombus, and bilateral pulmonary embolism in a second patient with lung disease progression.

Discussion

This work provided an extensive, comprehensive analysis of imaging, laboratory, pathologic, genetic, primary disease-related

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Table 4 Overview of Post-procedure Course of Patients Who Expired Within 3 Months Post-RAE

No.	Baseline Patient Characteristics	Post-RAE Course/Potential Reason of Death	Death Time
1.	Hx of HAIP; > 25%TB, bilobar liver disease; CEA = 766 ng/mL; EHD sites = 2	RAE-related major toxicity (grade 3-4 chest pain, SOB, pleural effusion in face of stable lung metastases 1 month post-RAE); managed conservatively. Death cancer-related, likely owing to liver failure with evidence of liver POD (1 month post-RAE) and EHD POD (lungs, lymph nodes).	1.93 months
2.	Hx of HAIP; bilobar liver disease, CEA = 1357 ng/ml; EHD sites = 4	RAE-related major toxicity: grade 4 SOB (acute hypersensitivity to steroids post-procedure), resolved. Cancer-related death in face of EHD POD 1 month post-RAE and liver POD on first follow-up; Hx of hemochromatosis.	1.53 months
3.	Hx of liver Rx and HAIP; > 25% TB, bilobar liver disease, CEA = 228 ng/mL; EHD sites = 2	Cancer-related death, likely owing to liver failure (ascites/grade 3 hyperbilirubinemia/anasarca) in face of liver POD (which precluded second RAE session), lung POD, and bilateral pulmonary embolism/pleural effusion/IVC and RHV thrombi 1-month post-RAE (treated with anticoagulation).	2.93 months
4.	Hx of HAIP; bilobar liver disease, CEA = 218 ng/mL	Unknown death reason; likely liver failure in face of RFA 1 month post-RAE with grade 4 hyperbilirubinemia/fever)	2.27 months
5.	Hx of liver Rx and HAIP; EHD sites = 1; ECOG = 1	RAE contributed to fatal outcome (dramatic increased of LFTs right post-RAE); also, liver POD, secondary biliary obstruction, coagulopathy, colitis, duodenal stenosis, required stenting, HBV.	1.27 months
6.	Hx of HAIP, mitomycin, ≥ 3 chemotherapy lines, bilobar disease, CEA = 4713 ng/mL	Death reason unknown, likely liver failure in patient with history of hemochromatosis (2 months post-RAE admitted for abdominal pain in outside hospital with biliary stricture, cirrhosis, ascites).	2.9 months
7.	Hx of liver Rx, HAIP, ≥ 3 chemotherapy lines, bilobar disease, EHD sites = 2	Post-RAE: ECOG decline (from 0 to 3, 5 days post-RAE). Could not proceed with planned second RAE session owing to grade 3 hyperbilirubinemia in face of liver POD on first follow-up.	2.47 months
8.	Hx of HAIP, ≥ 3 chemotherapy lines, bilobar disease, EHD sites = 2	Post-RAE: severe abdominal, back pain/anorexia/SOB/chest pain/phlegm 1 week post-RAE; 11 days post-RAE admitted for pneumonia, recovered. Death cancer-related (although no records within 3 weeks before death).	1.83 months
9.	Bilobar disease, CEA = 130 ng/mL; EHD sites = 2; ECOG = 1	Death cancer-related in face of untreated liver POD, peritoneal carcinomatosis, and not-RAE related adverse event (6 weeks post-RAE obstruction owing to stomach bleed (patient was on Xarelto) requiring transfusion; significant ECOG decline.	1.77 months
10.	Bilobar disease, EHD sites = 2; ECOG = 1	Grade 3-4 toxicity: Post-embolization syndrome. Six weeks post-RAE urosepsis, 2 months post-RAE: brain radiotherapy for brain metastases, then altered mental status/hypoxia owing to fluid overload, leptomeningeal metastases.	2.13 months
11.	Hx of HAIP; bilobar disease, CEA = 404 ng/mL; EHD sites = 1	No report of RAE-related toxicity and other adverse events after RAE.	2.3 months

Abbreviations: CEA = Carcinoembryonic antigen level; ECOG = performance status; EHD = extrahepatic disease; HAIP = hepatic artery infusion pump; HBV = hepatitis B; Hx = history; IVC = inferior vena cava; LFTs = liver function tests; POD = progression of disease; RAE = radioembolization; RFA = radiofrequency ablation; RHV = right hepatic vein; RT = radiotherapy; Rx = resection; SOB = shortness of breath; TB = tumor burden.

biomarkers, and procedure-related factors as well as prior and post-RAE therapies, associated with OS and LPFS following RAE of CLMs.

Overall Survival Prediction Nomogram

The developed nomogram included 6 easy-to-obtain pre-RAE parameters and provided a good prediction of patient survival post-RAE, based on internal bootstrap validation results: the nomogram showed good discrimination (c-index = 0.745) and calibration. One-year overall survival of patients with total nomogram points of < 25 versus > 80 was 90% and 10%, respectively.

An existing OS prediction nomogram, created by Fendler et al,²³ potentially suffered from selection bias owing to the inclusion of patients with very limited extrahepatic metastases and did not demonstrate any association of extrahepatic metastases with survival, contradictory to the reported negative impact of extrahepatic disease on patient survival post-RAE.²⁴⁻²⁶ Overall, 73% of the study patients had extrahepatic metastases at the time of RAE. Recent multicenter randomized phase III trials (FOXFIRE [registered with the ISRCTN registry, number ISRCTN83867919], SIRFLOX [ClinicalTrials.gov trial number: NCT00724503], and FOXFIRE-Global [ClinicalTrials.gov trial number: NCT01721954]) showed

no survival benefit when combining 90Y RAE with first-line chemotherapy.¹³ According to existing evidence, patients will continue to present for RAE at the latest stages of disease, especially when they progress in the liver while receiving second, third, or subsequent chemotherapy regimens. RAE is recommended in the chemo-refractory or salvage setting.¹ It is therefore important to identify and describe predictive factors in these settings. An OS prognostic score, developed by Damm et al, included heavily pre-treated patients, with a median baseline Karnofsky index of 80% and liver tumor load of 20%. The OS post-RAE was 6.7 months. This suggests that RAE was a relatively aggressive therapy for this specific compromised population.²⁷ In our study, only 3% of patients had ECOG grade 2 performance status and only 14% had ≥ 25% baseline liver involvement by tumor.

All increased metabolic tumor uptake parameters of most metabolically active tumor (SUVmax, SUVpeak, SUVmean, MTV, TLG) within the intended-to-treat region were significantly associated with decreased OS. Recent studies confirmed that 18F-FDG PET/CT is useful to evaluate treatment response, and it is an emerging prognostic tool in patients with CLM undergoing RAE, with semi-quantitative factors (such as MTV and TLG) correlating with survival better than RECIST criteria.^{28,29} We therefore

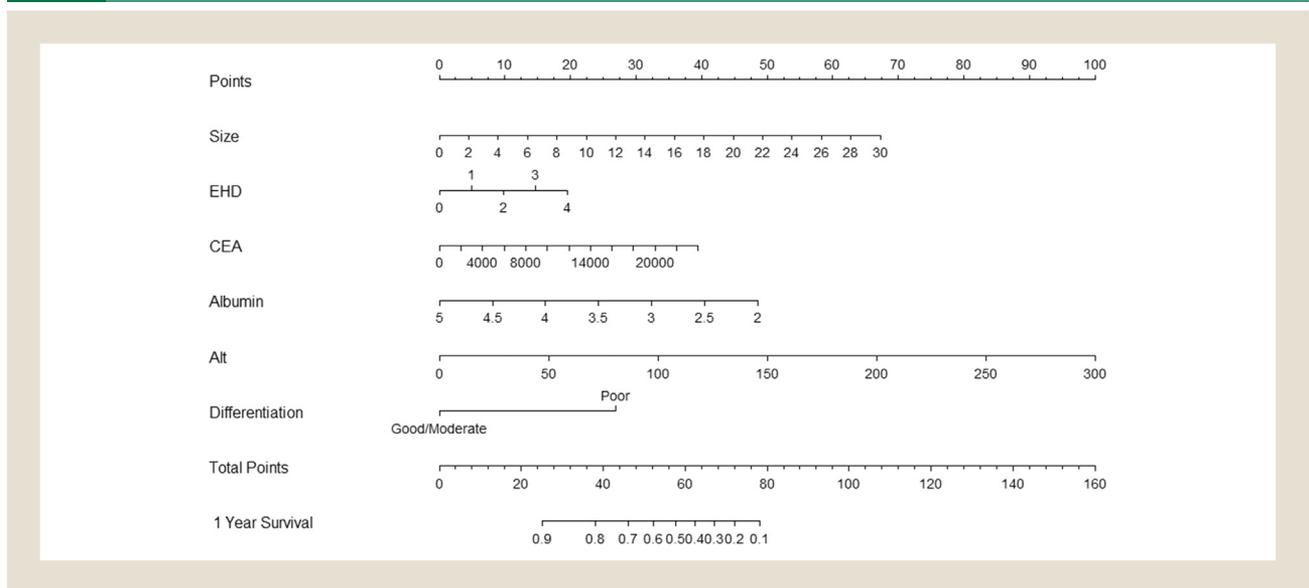
Table 5 Multivariate Analysis Result of Factors Associated With Overall Survival Post-RAE

	Variable Included in MVA	P Value	HR	95% CI
1	Tumor differentiation level (good/moderate vs. poor)	<.0001	5.3	2.6-10.7
2	Sum of largest diameters of two liver target lesions	<.0001	1.15	1.09-1.21
3	Number of EHD sites (range, 0-4)	.016	1.41	1.07-1.87
4	CEA level at time of RAE (ng/ml)	<.001	1.00009	1.00006-1.0001
5	Albumin (g/dL)	.005	0.46	0.27-0.79
6	Alanine aminotransferase (U/L)	<.0001	1.02	1.01-1.03
7	Lymphovascular invasion on pathology of primary (yes/no)	>.05	Excluded by stepwise forward selection	
8	Pre-RAE neutrophil/lymphocyte ratio	>.05	Excluded by stepwise forward selection	

Abbreviations: CEA = Carcinoembryonic antigen level; EHD = extrahepatic disease; RAE = radioembolization.

advocate metabolic imaging to always be performed before RAE. Prior investigations described anatomic biomarkers, such as CLM size, as predictors of decreased survival post-RAE.^{23,30-32} Measuring the sum of the 2 largest lesion diameters is also important for RECIST 1.1 evaluations and were part of our nomogram. Both anatomic (lesion size) or metabolic tumor parameters were statistically significant predictors of OS in this study. However, both factors could not be included into the nomogram because lesion size generally correlates with metabolic uptake. Thus, owing to the fact that 18F-FDG PET/CT is not always available in other institutions for treatment planning, we chose to include anatomic parameters into the nomogram.

ALT, unlike other routine liver panel enzymes, is predominantly found in the liver and released into the bloodstream as the result of liver injury, thus serves as a fairly specific indicator of liver damage. ALT was the most predictive nomogram factor of decreased survival: ALT level > 250 U/L alone corresponded to > 80 nomogram points, distinguishing patients with > 90% risk for death within 1 year after RAE. Other liver enzymes (aspartate aminotransferase and alkaline phosphatase) were also found to be associated with post-RAE survival. Because we could only include a limited number of factors in the MV analysis and the latter factors are less hepatic function-specific biomarkers compared with ALT, they were not included. Transaminase toxicity was predictive of survival post-RAE

Figure 1 Nomogram for Overall Survival Prediction after Radioembolization of Colorectal Cancer Liver Metastases

Abbreviations: Alt = Alanine aminotransferase (U/L); CEA = carcinoembryonic antigen level (ng/mL); differentiation = tumor differentiation level; EHD = number of extrahepatic disease sites; Size = sum of largest diameters of 2 largest liver lesions in intended-to-treat-region. **Example 1** of nomogram points calculation. The patient presented for radioembolization with following parameters: sum of 2 largest liver lesions diameters of 11.1 cm; 2 sites of extrahepatic disease; CEA = 765.6 ng/mL; albumin = 2.3 g/dL; ALT = 27 U/L; and poor tumor differentiation level. By drawing a straight line from the 11.1 cm point on the Size axis of the nomogram to the Points axis we find that a lesion of 11.1 cm corresponded to 25 points. Repeating the same for the other variables, we got 10 points for 2 sites of extrahepatic disease, 1 point for CEA = 765.6 ng/mL, 45 points for albumin = 2.3 g/dL, 9 points for ALT = 27 U/L, and 27 points for poor tumor differentiation. The sum of these points was 117 and again drawing a straight line from 117 on the Total Points axis to the 1-Year Survival prediction axis, we obtained < 10% as the predicted probability of 1-year survival for this patient. The patient had an actual overall survival of 1.9 months. **Example 2** of nomogram points calculation. The patient had the following baseline characteristics: sum of 2 largest liver lesions diameters of 1.8 cm, no extrahepatic disease, CEA = 2.9 ng/mL, albumin = 4.5 g/dL, ALT = 34 U/L, and moderate tumor differentiation level. By drawing a straight line from the 1.8 cm point on the Size axis of the nomogram to the Points axis, we find that a sum of lesions diameters of 1.8 cm corresponded to 4 points. Repeating the same for the other variables, we got 0 points for no extrahepatic disease, 0 points for CEA = 2.9 ng/mL, 9 points for albumin = 4.5 g/dL, 12 points for ALT = 34 U/L, and 0 points for moderate tumor differentiation. The sum of these points was 25, and again drawing a straight line from 25 on the Total Points axis to the 1-Year Survival prediction axis, we obtained 90% as the predicted probability of 1-year survival for this patient. The patient had actual overall survival of 60.3 months.

Table 6 Post-RAE Toxicities

Toxicities	n/N (%)
Grade 1-2 toxicities	
1. Fatigue/weakness	43/102 (42)
2. Abdominal pain/distension	23/102 (23)
3. Constipation/diarrhea	14/102 (14)
4. Fever	11/102 (11)
5. Change in appetite/weight changes	11/102 (11)
6. Nausea	10/102 (10)
7. Light colored stool/dark urine	10/102 (10)
8. Shortness of breath	10/102 (10)
9. Ascites	5/102 (5)
10. Vomiting	4/102 (4)
11. Shoulder/back pain	4/102 (4)
12. Hiccups	1/102 (1)
13. Portal hypertension	1/102 (1)
14. Portal hypertension/ascites in patient with prior oxaliplatin administration	1/102 (1)
Total grade 1-2 toxicities	44/102 (43)
Grade 3-4 toxicities	
1. Post-RAE syndrome (at 1-90 days)	5/102 (5)
2. Grade 3 abdominal pain/distension (at 10-12 days)	3/102 (3)
3. Grade 3 fevers (at 3 days)	1/102 (1)
4. Acute liver failure/failure to thrive/grade 3 hyperbilirubinemia (at 14 days)	1/102 (1)
5. Grade 3 dyspnea (at 30 days)	1/102 (1)
6. Biliary obstruction + Budd-Chiari syndrome + stop chemotherapy for 6 weeks (at 1 day/60 days)	1/102 (1)
7. Biloma requiring multiple drainages, liver abscess, E. Faecium sepsis; patient with liver POD (at 5 days)	1/102 (1)
8. Post-mapping brain infarction owing to anticoagulation break in patient with history of atrial fibrillation. Post-procedure hypertension, recurrent atrial fibrillation, abdominal pain, hypotension, fever, required overnight admission (at 1 day)	1/102 (1)
Total grade 3-4 toxicities	14/102 (14)

Abbreviations: POD = Progression of disease; RAE = radioembolization. One patient was lost to follow-up post-procedure; multiple complications possible per patient.

in prior studies^{23,33}; thus it should be emphasized as an important patient selection criterion in patients with CLM. Total bilirubin level was not predictive of survival in our study, most likely owing to the strict inclusion criteria of RAE in our center. Only patients with total bilirubin ≤ 1.5 mg/dL were eligible for RAE. Commonly, patients with bilirubin < 2 mg/dL are considered eligible for RAE.³⁴

CEA levels differed dramatically in this cohort, with a median of 52 ng/mL, ranging from normal level to $> 20,000$ ng/mL, considered as an outlier in our study that contributed to very high CEA values in the nomogram. Increased CEA level has been associated with poorer survival post-RAE of CLM in multiple studies^{4,28,33,35}; however, this is influenced by multiple factors, including tumor differentiation level, liver function, and the side of primary tumor.³⁵

The OS predictors in this study are similar to a recent study, where higher CEA and aspartate aminotransferase (AST) level, NLR > 5 , extrahepatic disease, and larger volume of liver metastases were independently associated with increased risk of death on multivariate analysis.³⁶

The median OS in this cohort was 11.3 months post-RAE. This compares favorably with large retrospective studies, with reported median survivals of 7.2 to 10.6 months after RAE of CLM, mostly in the salvage setting.³⁷⁻⁴⁰ It should be noted that RAE in this cohort was administered at a median of 30.9 months from the initial diagnosis of CLM. This reflects that most patients were heavily pretreated and received multiple prior liver-directed therapies, including resection, hepatic artery infusion pump (HAIP), and ablation. Pre-RAE therapies were not associated with OS, although the fact that most patients received loco-regional therapies pre-RAE might have influenced that. The actual liver function and parameters indicating underlying hepatic toxicity (albumin and ALT level) and the metastatic disease volume (liver tumor(s) size, extrahepatic disease, extent and CEA level), as well as tumor differentiation, were significant predictors of post-RAE OS.

All analyzed post-RAE therapies (increased number of systemic chemotherapy lines, HAIP, ablation, and bevacizumab) were associated with increased OS post-RAE. This result is concordant with prior studies, where RAE did not prohibit re-initiation of systemic chemotherapy, HAIP therapy, or ablation for CLM that persisted or progressed after initial response to RAE.^{4,9,12,41-43} This also demonstrated that OS post-RAE cannot be attributed solely to RAE, but rather to the overall management of the disease in the salvage setting. Post-RAE therapies were not included in the 1-year OS prediction nomogram. This was necessary to allow us to reach our goal of patient stratification before RAE in this setting.

Patients with KRAS or PI3KCA mutations and left-sided primary tumors showed decreased OS following RAE in our study; however, the difference was not statistically significant. Patients with BRAF mutation and right-sided primary tumor showed increased post-RAE survival, but again, not statistically significantly.

Predictors of LTP and LPFS

The ORR of 52% in this study compares favorably with published data of 10% to 48% response rates, depending on whether the patients received RAE with second-line chemotherapy or at the salvage setting.^{10,17,19,20,44} Baseline SUVmax was the only significant predictor of LPFS on MV analysis. There was no significant difference in LPFS for those who received resin or glass microspheres. Although the incidence of stasis, resulting in suboptimal radiation dose delivery to tumor, increased the risk of local tumor progression, it did not reach statistical significance. PI3KCA mutation was not a significant predictor of LPFS in this cohort, unlike in a prior study.⁴⁵ This could be related to differences in methodology between studies (response evaluation criteria, evaluation of local tumor progression, rather than LPFS and analysis of different PI3K mutations, associated with gain of function).

Safety of 90Y RAE

RAE had an acceptable safety profile in this series, with an incidence of grade 3 to 4 toxicities of 14%, a median OS of 11.3

months, no death within 30 days post-procedure, and no RAE-related death within 3 months posttreatment.

Two patients in this study developed liver venous occlusion post-RAE: Budd-Chiari syndrome in 1 patient and right hepatic vein, inferior vena cava thrombus, and bilateral pulmonary embolism in the second patient. Radiation therapy was shown to cause endothelial activation with subsequent pro-thrombotic response and tissue inflammation with subsequent vein external compression, stasis, and thrombus formation.⁴⁶ However, the number of patients with these complications was too small to draw meaningful conclusions regarding liver venous occlusion association with RAE.

Study Limitations

The limitations of this study included the single-center retrospective study design with its inherited limitations and a relatively short follow-up time. Also, there was a lack of external nomogram validation, which preferably would include prospectively recruited patients at multiple centers. Finally, the actual radiation dose delivered to the tumor could not be measured in this study owing to technical limitations; thus, it could not be analyzed as a prognosticator of RAE.

Conclusion

The developed nomogram included 6 pre-RAE parameters and provided good prediction of patient survival post-RAE. Baseline SUVmax was the single significant predictor of LPFS on MV.

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