

# Survival and Toxicities after $^{90}\text{Y}$ Transarterial Radioembolization of Metastatic Colorectal Cancer in the RESIN Registry

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Conflicts of interest are listed at the end of this article.

See also the editorial by Liddell in this issue.

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**Background:** Patients with unresectable, chemorefractory hepatic metastases from colorectal cancer have considerable mortality. The role of transarterial radioembolization (TARE) with yttrium 90 ( $^{90}\text{Y}$ ) microspheres is not defined because most reports are from a single center with limited patient numbers.

**Purpose:** To report outcomes in participants with colorectal cancer metastases treated with resin  $^{90}\text{Y}$  microspheres from a prospective multicenter observational registry.

**Materials and Methods:** This study treated enrolled adult participants with TARE using resin microspheres for liver-dominant metastatic colorectal cancer at 42 centers, with enrollment from July 2015 through August 2020. TARE was used as the first-, second-, or third-line therapy or beyond. Overall survival (OS), progression-free survival (PFS), and toxicity outcomes were assessed by line of therapy by using Kaplan-Meier analysis for OS and PFS and Common Terminology Criteria for Adverse Events, version 5, for toxicities.

**Results:** A total of 498 participants (median age, 60 years [IQR, 52–69 years]; 298 men [60%]) were treated. TARE was used in first-line therapy in 74 of 442 participants (17%), second-line therapy in 180 participants (41%), and third-line therapy or beyond in 188 participants (43%). The median OS of the entire cohort was 15.0 months (95% CI: 13.3, 16.9). The median OS by line of therapy was 13.9 months for first-line therapy, 17.4 months for second-line therapy, and 12.5 months for third-line therapy ( $\chi^2 = 9.7$ ;  $P = .002$ ). Whole-group PFS was 7.4 months (95% CI: 6.4, 9.5). The median PFS by line of therapy was 7.9 months for first-line therapy, 10.0 months for second-line therapy, and 5.9 months for third-line therapy ( $\chi^2 = 8.3$ ;  $P = .004$ ). TARE-attributable grade 3 or 4 hepatic toxicities were 8.4% for bilirubin (29 of 347 participants) and 3.7% for albumin (13 of 347). Grade 3 and higher toxicities were greater with third-line therapy for bilirubin ( $P = .01$ ) and albumin ( $P = .008$ ).

**Conclusion:** Median overall survival (OS) after transarterial radioembolization (TARE) with yttrium 90 microspheres for liver-dominant metastatic colorectal cancer was 15.0 months. The longest OS was achieved when TARE was part of second-line therapy. Grade 3 or greater hepatic function toxicity rates were less than 10%.

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Colorectal cancer is the fourth most common malignant neoplasm and third leading cause of cancer mortality in the United States, with an overall lifetime risk of 4.3% for men and 4.0% for women (1,2). There were an expected 149 500 new cases and 52 980 colorectal cancer–related deaths in 2021 (2). The liver is the most common site of metastasis, with up to 70% of patients developing hepatic

involvement (3). Although surgical resection remains the standard treatment, only 20% of patients present with resectable disease (4). Despite improvements in chemotherapeutic and biologic agents, the 5-year overall survival (OS) in the setting of unresectable metastatic disease is 14% (2). Once metastases become chemorefractory, the median OS ranges between 4 and 5 months (4–7).

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## Abbreviations

OS = overall survival, PFS = progression-free survival, RECIST = Response Evaluation Criteria in Solid Tumors, RESIN = Radiation-Emitting SIR-Spheres in Non-Resectable Liver, TARE = transarterial radioembolization

## Summary

Transarterial radioembolization with yttrium 90 microspheres resulted in 15.0-month overall survival in 498 participants with metastatic colorectal cancer: 17.4 months when integrated with second-line treatment and 12.5 months when integrated with salvage treatment.

## Key Results

- In a prospective observational cohort of 498 participants with metastatic colorectal cancer treated with transarterial radioembolization (TARE) with yttrium 90–labeled microspheres, the median overall survival (OS) was 15.0 months.
- The median OS by line of therapy when TARE was used was 13.9 months in first-line therapy, 17.4 months in second-line therapy, and 12.5 months in third-line therapy ( $\chi^2 = 9.7$ ;  $P = .002$ ).
- Grade 3 or greater TARE-attributable hepatic function toxicity rates were less than 10%.

Patients with liver-dominant metastases who progress on chemotherapy regimens may be considered for local-regional therapies, such as transarterial radioembolization (TARE) with yttrium 90 ( $^{90}\text{Y}$ )–labeled microspheres. TARE improved progression-free survival (PFS) in a phase III trial when combined with second-line chemotherapy (8) and resulted in a median OS between 9.5 and 10.6 months for salvage therapy after second-line therapy (5,9–11). Most reports of TARE for metastatic colorectal cancer are retrospective and from a single center, which limits the identification of the optimal role of TARE in patients with liver-dominant metastatic colorectal cancer.

The source of data for this report was the Radiation-Emitting SIR-Spheres in Non-Resectable (RESIN) Liver Tumor Patient Study. The primary goal of our study was to analyze outcomes in the 498 participants treated with TARE in different lines of therapy in real-world practice settings with use of the prospective multicenter observational data from the registry.

## Materials and Methods

### Participants

Patients with metastatic colorectal cancer treated with radioembolization were enrolled in a prospective observational cohort, the RESIN registry (ClinicalTrials.gov identifier NCT02685631) between July 2015 and August 2020. The study was funded by Sirtex Medical, which participated in the study design and data collection. The RESIN registry, a prospective observational database, was approved by the institutional review board at each of the enrolling sites. All participants signed informed written consent. The study complies with the Health Insurance Portability and Accountability Act. The authors made decisions regarding participant

enrollment, data analysis and interpretation, and manuscript writing and submission.

Inclusion criteria were age 18 or older, the ability to provide informed consent without need for a surrogate, and being deemed appropriate for TARE at the treating institution. Physicians at each of the institutions determined appropriateness for treatment based on tumor burden, distribution, and liver function tests, including bilirubin, albumin, aspartate aminotransferase, alanine aminotransferase, and international normalized ratio. Eastern Cooperative Oncology Group performance status and hepatic tumor burden were assessed.  $^{90}\text{Y}$  dose activity and follow-up imaging and laboratory examinations were performed per local practice guidelines (Appendix E1 [online]). Key exclusion criteria included age younger than 18 years, an inability to provide informed consent, and having previously undergone radioembolization.

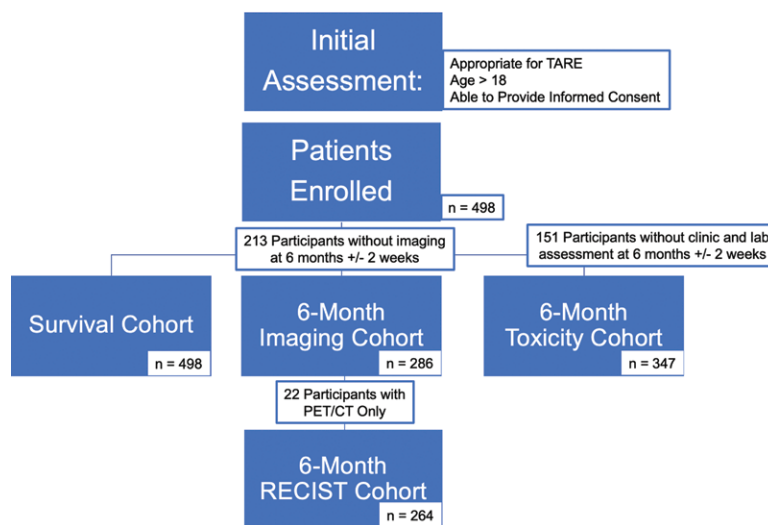
### Centers

Forty-two centers enrolled participants, with the principal investigator (D.B.B.) at the coordinating center (Table E1 [online]). There was a separate publication steering committee (A.S.K., L.M., D.Y.S.), which assisted with study design, data review, and manuscript editing. Twenty-six of the hospitals were academic, with an on-campus medical school and radiology residency program. The other 16 programs did not have one or both of those characteristics. Participants were enrolled on the day of treatment and tracked afterward. All enrolled participants were included in the analysis.

### Procedures

Prior hepatic interventions, such as resection, chemoembolization, ablation, and stereotactic body radiation therapy, were tracked. Previous systemic therapy agents were documented, including chemotherapy and biologic and immunologic agents.

All participants were treated by interventional radiologists (H.K., R.T.G., Z.S.C., R.O., N.M.A., E.A.W., C.G., J.S.B.,



**Figure 1:** Flowchart of enrolled participants for survival analysis, response analysis, and toxicity analysis. Participants were tracked until they died or left the study. Imaging and toxicity were assessed for related studies at 6 months plus or minus 2 weeks. RECIST = Response Evaluation Criteria in Solid Tumors, TARE = transarterial radioembolization.

**Table 1: Baseline Characteristics**

Characteristic	Value
Sex (n = 498)	
F	200 (40)
M	298 (60)
Age (y) (n = 498)	
Overall*	60 (52–69)
Women†	59 ± 12 (31–89)
Men†	61 ± 13 (20–93)
BMI (n = 479)‡	27 (23–31)
Tumor burden (n = 450)	
≤10%	210 (47)
11%–25%	115 (26)
≥26%	125 (28)
ECOG performance status (n = 472)	
0—Fully active	253 (54)
1—Restricted	188 (40)
2—Ambulatory	26 (5.5)
3—Capable	5 (1.1)
4—Disabled	0
Extrahepatic disease (n = 475)	
Present	180 (38)
Absent	295 (62)
Baseline albumin (g/dL) (n = 484)	
≤3	45 (9.3)
>3	439 (91)
Baseline bilirubin (mg/dL) (n = 484)	
≤1.5	470 (97)
>1.5	14 (2.9)

Note.—Unless otherwise specified, data are numbers of participants, with percentages in parentheses. BMI = body mass index, ECOG = Eastern Cooperative Oncology Group.

\* Age for the overall study sample is reported as the median, with IQR in parentheses.

† Data are means ± SDs, with ranges in parentheses.

‡ BMI is reported as the median, with the IQR in parentheses. BMI is calculated as weight in kilograms divided by height in meters squared.

**Table 2: Previous Treatment**

Characteristic	No. of Participants
Prior lines of chemotherapy (n = 442)	
0	74 (17)
1	180 (41)
2 or more	188 (43)
Prior biologic agents (n = 442)	
0	89 (20)
1	263 (60)
2	76 (17)
3	9 (2.0)
4	5 (1.1)
Prior immunologic agents (n = 442)	
0	436 (99)
1	5 (1.1)
2	1 (0.2)
Prior hepatic surgery (n = 481)	67 (14)
Prior arterial embolization (n = 485)	28 (5.8)
Prior portal vein embolization (n = 485)	8 (1.6)
Prior ablation (n = 485)	68 (14)
Prior SBRT (n = 485)	27 (5.6)

Note.—Data in parentheses are percentages. SBRT = stereotactic body radiation therapy.

S.R.P., A.K.A.A., J.G., D.Y.S., D.B.B.) with 7–27 years of experience (Appendix E1 [online]). Participants underwent scintigraphy with technetium 99m-labeled macroaggregated albumin to ensure lung dose of less than 30 Gy as well as absence of extrahepatic deposition. Participants then underwent treatment with resin <sup>90</sup>Y microspheres (SIR-Spheres, Sirtex Medical), which are approved by Food and Drug Administration for the treatment of colorectal cancer liver metastases.

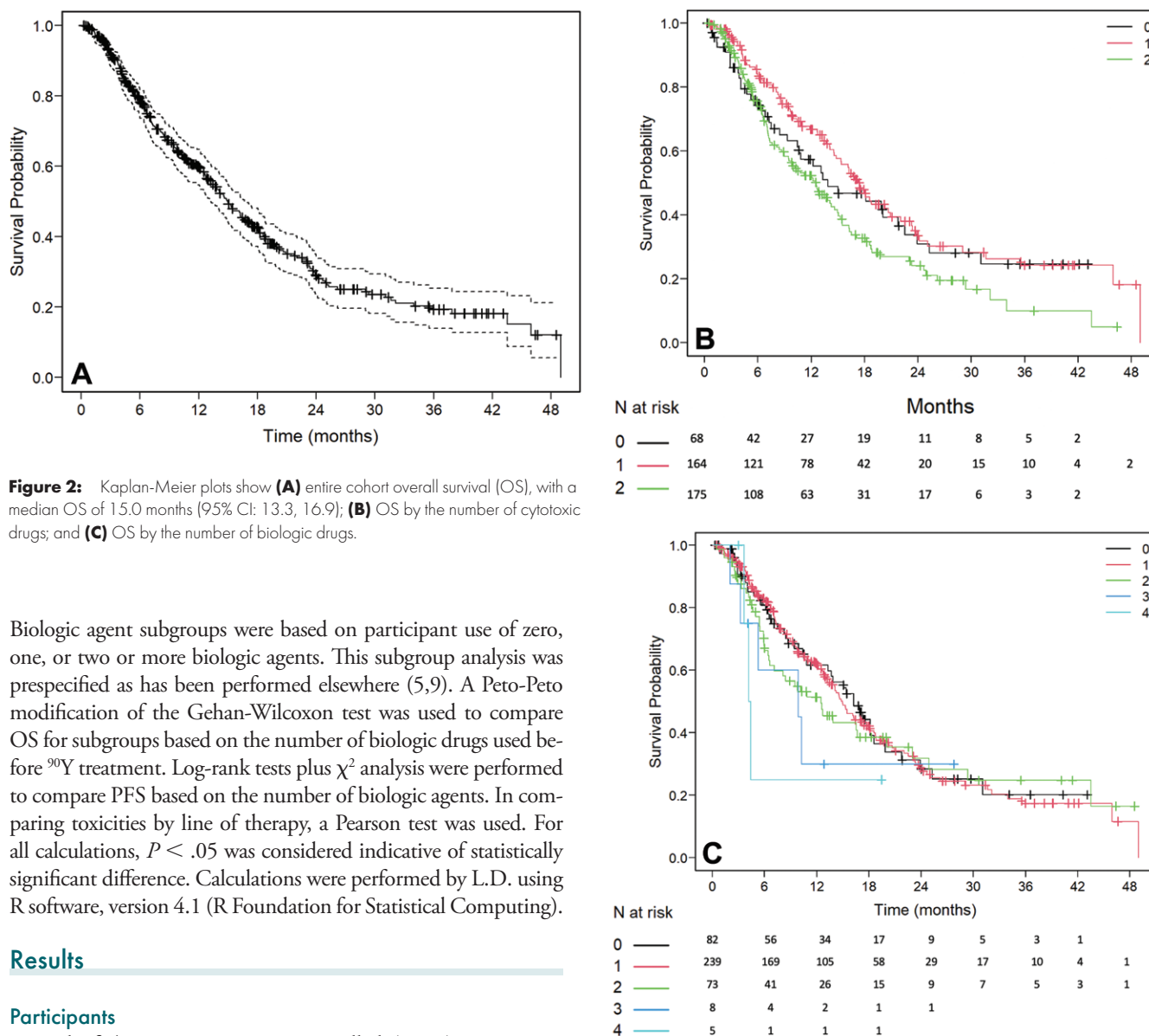
### Outcomes

All participants were tracked until death, last follow-up, or the conclusion of the study. These participants constituted the survival cohort. Individual institutional protocols were used to schedule clinic visits, follow-up laboratory tests, and response imaging assessments (Appendix E1 [online]). Response imaging, toxicity, and laboratory assessments, including liver function tests, were evaluated using available data at 6 months plus or mi-

nus 2 weeks. This time point was selected to limit confounding effects from additional chemotherapy based on the PFS reported in prior prospective studies (8,12). Tumor response evaluation was performed using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Participants with imaging or toxicity assessment at 6 months plus or minus 2 weeks constituted the 6-month RECIST imaging and toxicity cohorts, respectively. The objective response rate was defined as the sum of complete and partial responses. The disease control rate was defined as the sum of the objective response rate plus stable disease. The best response was assessed in the first 6 months after treatment. Intrahepatic progression and extrahepatic progression were recorded. Intrahepatic progression was defined as either development of new or growth of treated hepatic metastases. Extrahepatic progression was defined as development of new or growth of new disease outside the liver. All liver function and grade 3 or greater constitutional toxicities were assessed using the Common Terminology Criteria for Adverse Events, version 5. Hepatic function toxicities were attributable to TARE in the absence of hepatic progression (13).

### Statistical Analysis

Kaplan-Meier curves with 95% CIs were constructed for OS, PFS, and hepatic PFS. Differences between subgroups were assessed with  $\chi^2$  tests. Because the data were from a registry, the lack of randomization left the groups unequally distributed. At data assessment, log-rank tests were applicable given the number of participants who reached OS and PFS. Survival was tracked beginning from the day of enrollment. Subgroups were created based on lines of chemotherapy, and log-rank tests plus  $\chi^2$  analysis were performed to evaluate differences between subgroups.



**Figure 2:** Kaplan-Meier plots show (A) entire cohort overall survival (OS), with a median OS of 15.0 months (95% CI: 13.3, 16.9); (B) OS by the number of cytotoxic drugs; and (C) OS by the number of biologic drugs.

Biologic agent subgroups were based on participant use of zero, one, or two or more biologic agents. This subgroup analysis was prespecified as has been performed elsewhere (5,9). A Peto-Peto modification of the Gehan-Wilcoxon test was used to compare OS for subgroups based on the number of biologic drugs used before  $^{90}\text{Y}$  treatment. Log-rank tests plus  $\chi^2$  analysis were performed to compare PFS based on the number of biologic agents. In comparing toxicities by line of therapy, a Pearson test was used. For all calculations,  $P < .05$  was considered indicative of statistically significant difference. Calculations were performed by L.D. using R software, version 4.1 (R Foundation for Statistical Computing).

## Results

### Participants

A total of 498 participants were enrolled (Fig 1). Participant demographics and baseline hepatic functions are outlined in Table 1, which includes available data points for each metric. The median age was 60 years (IQR, 52–69), with 298 men (60%) and 200 women (40%). The estimated tumor burden was 10% or less in 210 of 450 participants (47%), 11%–25% in 115 of 450 participants (26%), and 26% or more in 125 of 450 (28%) participants. Thirty-eight percent of participants (180 of 475) had extrahepatic metastases present at enrollment.

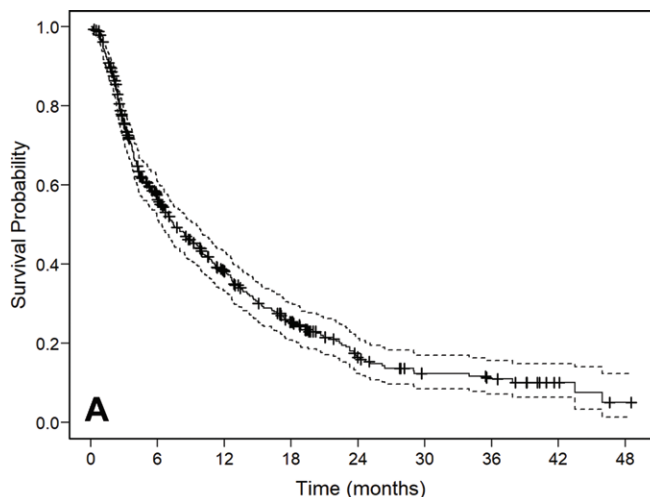
Previous treatments are described in Table 2. Data on previous chemotherapy and use of biologic agents were available in 442 of 498 participants (89%). Seventy-four of 442 participants (17%) underwent TARE as part of first-line therapy, including 44 (10%) who underwent TARE as the sole initial treatment of liver metastases. A total of 180 of 442 participants (41%) underwent TARE as part of second-line therapy and 188 (43%) after progression on second-line therapy. A total of 263 of 442 (60%) received one biologic agent before TARE, 76 (17%) received two biologic agents, and 14 (3.2%) received three or more biologic agents. Six of the 442 participants (1.4%)

received immunotherapy agents. Further evaluation of immunotherapy was not performed. Sixty-seven of 481 participants (14%) had undergone prior hepatic resection, whereas 28 of 485 (5.8%) underwent arterial embolization, 68 of 485 (14%) underwent prior ablation to the liver, and 27 of 485 (5.6%) underwent stereotactic body radiation therapy. Including resection, 50 of 498 participants (10%) had more than one liver-directed therapy before TARE.

### Procedure: TARE with $^{90}\text{Y}$ Microsphere Treatment

Dosimetry method data were available in 241 of 498 participants (48%). The most frequent technique was the body surface area method, which was used in 210 of 241 participants (87%). Whole-liver therapy was the most common treatment (257 of 485 participants [53%]), followed by lobar therapy (218 of 485 [45%]). Ten of 485 participants (2.1%) underwent segmental treatment. Participants undergoing whole-liver





**Figure 3:** Kaplan-Meier plots show (A) entire cohort progression-free survival (PFS), with a median PFS of 7.4 months (95% CI: 6.4, 9.5); (B) PFS by the number of cytotoxic drugs; and (C) PFS by the number of biologic drugs.

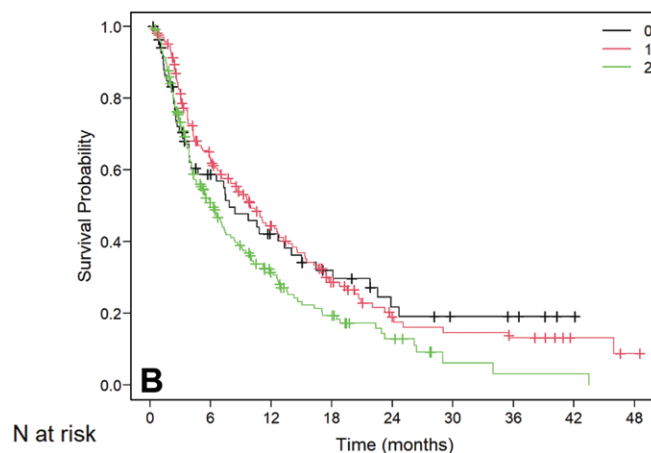
therapy were most commonly treated using a sequential lobar approach in two visits (230 of 257 [89%]). The median prescribed activity was 1.5 GBq (IQR, 1.1–2.0 GBq).

### Outcomes

**Survival cohort.**—The median OS of the entire cohort after TARE was 15.0 months (95% CI: 13.3, 16.9) (Fig 2A). We found a difference in median OS for first-line therapy of 13.9 months (95% CI: 9.3, 22.5), second-line therapy of 17.4 months (95% CI: 14.6, 20.7), and third-line therapy of 12.5 months (95% CI: 9.0, 14.6) ( $\chi^2 = 9.7$ ;  $P = .002$ ) (Fig 2B). We did not identify a difference in the median OS stratified by use of no biologic drugs (OS, 16.3 months [95% CI: 10.8, 18.6]), one biologic drug (OS, 15.0 months [95% CI: 13.2, 17.4]), or two or more biologic drugs (OS, 12.5 months [95% CI: 6.6, 20.0]) before  $^{90}\text{Y}$  therapy ( $\chi^2 = 2.2$ ;  $P = .10$ ) (Fig 2C). OS in the absence of extrahepatic metastases was 16.2 months (95% CI: 13.9, 18.6) compared with 12.6 months (95% CI: 8.6, 16.9) with disease outside the liver ( $\chi^2 = 2.5$ ;  $P = .10$ ).

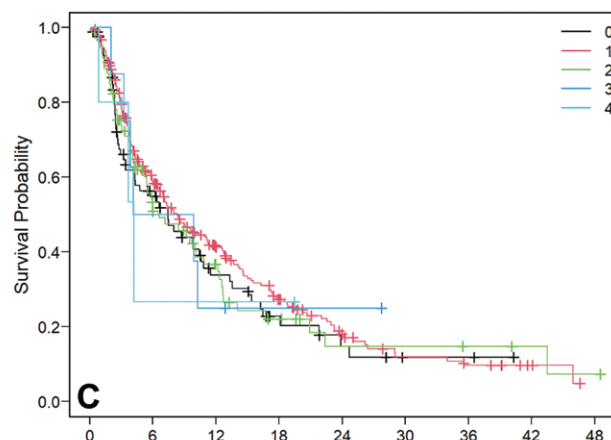
The median PFS for the entire cohort was 7.4 months (95% CI: 6.4, 9.5) (Fig 3A). We identified a difference in median PFS for first-line therapy of 7.9 months (95% CI: 3.9, 14), second-line therapy of 10.0 months (95% CI: 7.1, 12.7), and third-line therapy of 5.9 months (95% CI: 4.3, 7.5) ( $\chi^2 = 8.3$ ;  $P = .004$ ) (Fig 3B). The median PFS was 7.4 months (95% CI: 4.3, 10.6) in the subgroup that used no biologic agents, 8.3 months (95% CI: 6.7, 11.2) in the subgroup that used one biologic agent, and 6.6 months (95% CI: 4.3, 10.9) in the subgroup that used two or more biologic agents ( $\chi^2 = 3.1$ ;  $P = .50$ ) (Fig 3C). PFS in the absence of extrahepatic metastases was 7.5 months (95% CI: 6.6, 9.9) compared with 6.5 months (95% CI: 4.8, 10.0) for those with disease outside the liver ( $\chi^2 = 0.4$ ;  $P = .50$ ).

Median hepatic PFS for the entire cohort was 7.9 months (95% CI: 6.6, 9.8) (Fig 4A). We identified a difference in



N at risk

0	68	32	21	14	8	5	4	1
1	164	91	53	28	13	10	8	3
2	175	74	37	20	9	2	1	1

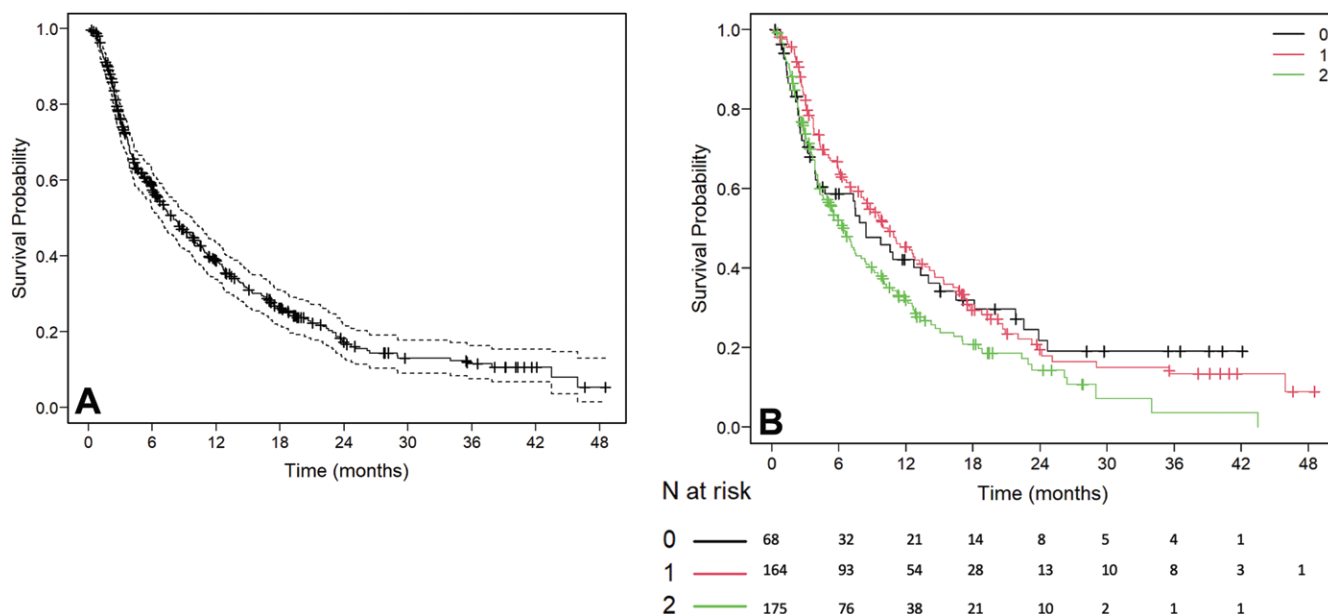


N at risk

0	82	38	19	9	5	2	2	
1	239	124	71	42	20	11	8	3
2	73	30	18	9	4	4	3	2
3	8	4	2	1	1			1
4	5	1	1	1				

hepatic PFS for first-line therapy of 8.4 months (95% CI: 3.9, 14.0), second-line therapy of 10.4 months (95% CI: 8.0, 13.2), and third-line therapy of 6.4 months (95% CI: 4.6, 8.0) ( $\chi^2 = 7.8$ ;  $P = .005$ ) (Fig 4B).

**Six-month RECIST imaging cohort.**—Follow-up imaging evaluation information with RECIST, version 1.1, response was available in 264 of 498 participants (53%) at 6 months plus or minus 2 weeks after  $^{90}\text{Y}$  treatment (Table 3). Of the 264 participants, four (1.5%) had complete response, 77 (29%) had partial response, and 98 (37%) had stable disease (Fig 5). Imaging modalities were CT in 206 of 264 (78%) and MRI in 58 of 264 (22%). Twenty-two additional participants had PET imaging only, which did not allow for RECIST assessment. The objective response rate was 31% (81 of 264), and the disease control rate was 68% (179 of 264). Eighty-five of 264 participants (32%) had progressive disease at 6 months (Fig 6). Of those with progressive disease, 79



**Figure 4:** Kaplan-Meier plots show (A) entire cohort hepatic progression-free survival (PFS), with a median of 7.9 months (95% CI: 6.6, 9.8), and (B) hepatic PFS by the number of cytotoxic drugs.

(93%) had intrahepatic progression. Thirteen participants (16%) with intrahepatic progression developed new disease within the treated zone of the liver, whereas 66 (84%) developed new hepatic disease outside the treated portion of the liver. New extrahepatic disease was present in 64 participants (24%), with the most common sites being the lungs (34 of 264 participants [13%]), lymph nodes (10 of 264 [3.8%]), and bones (eight of 264 [3.0%]).

### Progression and Death

A total of 325 of 498 participants (65%) left the study. Of these, at the time of data compilation, 253 participants (78%) died, 32 (9.8%) entered hospice, 11 (3.4%) left to seek treatment elsewhere, and 26 (8.0%) were lost to follow-up. The remaining 173 of 498 participants (35%) continued with the study. Of the participants who died, the cause of death was known for 151 of 253 (60%). Five deaths (2.0%) occurred within 30 days of  $^{90}\text{Y}$  therapy and were attributed to radiation-induced hepatic failure. Otherwise, disease progression was the most common cause of death (112 of 151 participants [74%]).

### Six-month Toxicity Cohort

Six months plus or minus 2 weeks after  $^{90}\text{Y}$  treatment, toxicity data were available in 347 participants (70%). TARE-attributable grade 3 or greater hepatic and all constitutional toxicities are included in Table 4. Of note, 16 of 29 TARE-attributable bilirubin toxicities (55%) were in participants undergoing TARE as part of third-line or greater treatment ( $P = .01$  compared with first and second line). Seven of 13 participants (54%) who developed TARE-attributable grade 3 or 4 albumin toxicities also received TARE as part of third-line or greater treatment ( $P = .008$  compared with first and second line). No dominant extrahepatic toxicities were reported.

**Table 3: Six-month Imaging Response**

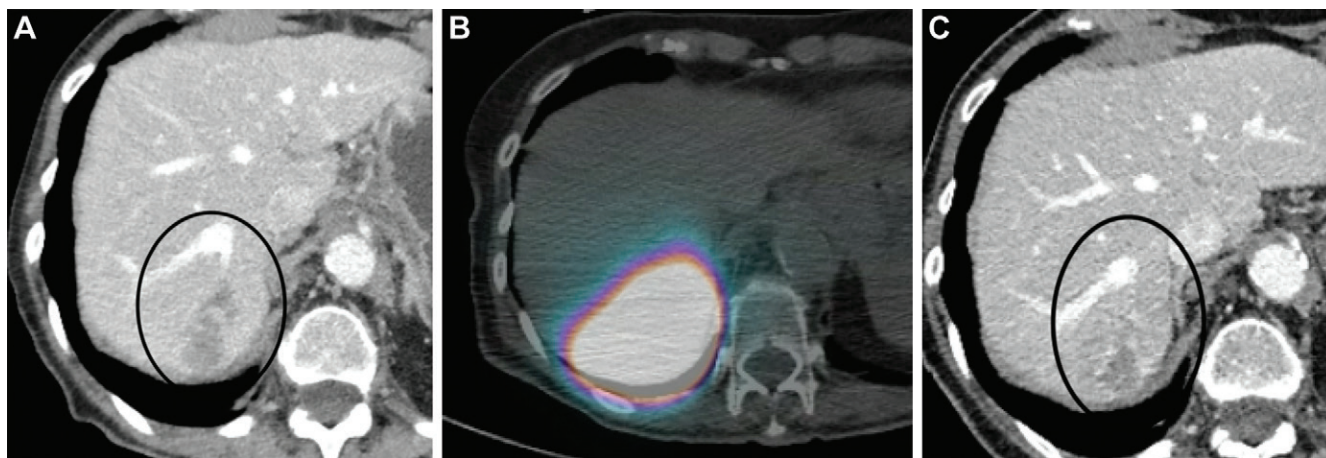
Parameter	No. of Participants
Imaging response ( $n = 286$ )	
Complete response	4 (1.4)
Partial response	77 (27)
Stable disease	98 (34)
Progressive disease	85 (30)
Data unavailable*	22 (7.8)
New extrahepatic disease ( $n = 286$ )	
Absent	222 (78)
Present	64 (22)
Location of new disease ( $n = 64$ )	
Bones	8 (12)
Esophagus	1 (1.6)
Large bowel	2 (3.1)
Lungs	34 (53)
Lymph nodes	10 (16)
Peritoneum	4 (6.3)
Other	5 (7.8)

Note.—Data in parentheses are percentages.

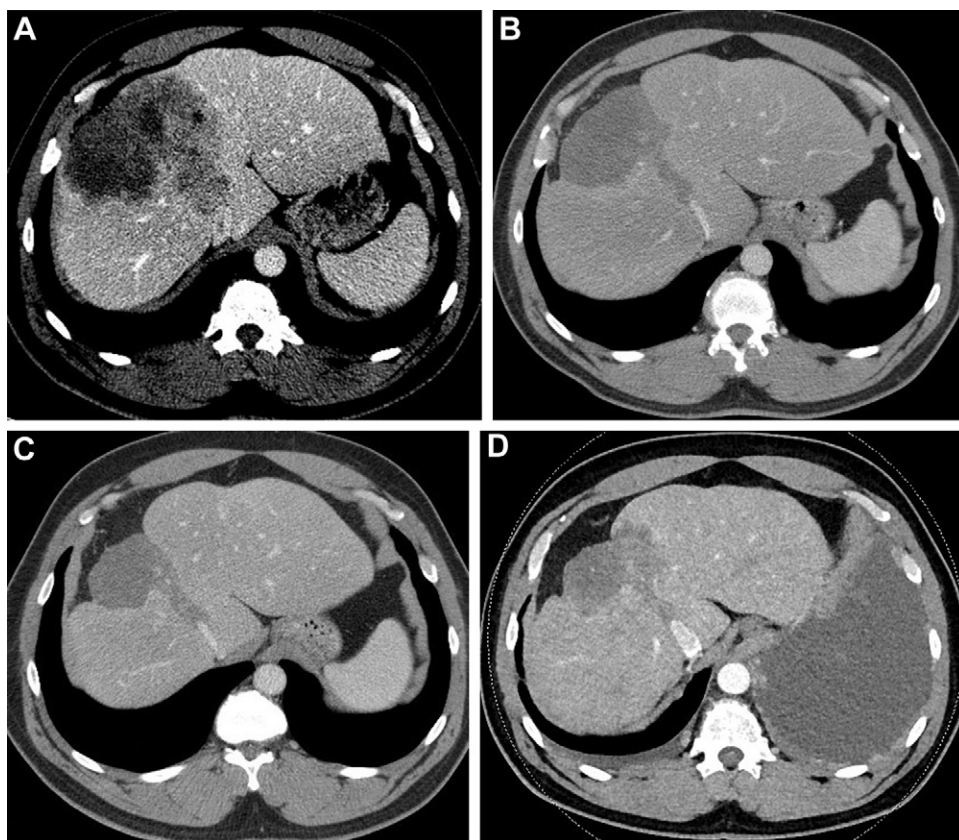
\* Participants were evaluated with PET alone, which did not allow Response Evaluation Criteria in Solid Tumors assessment.

### Discussion

The goal of our study was to assess survival, imaging, and toxicity outcomes after transarterial radioembolization (TARE) with yttrium 90 microspheres in 498 participants with metastatic colorectal carcinoma by using a multicenter prospective observational registry. Median overall survival (OS) was 17.4 months when TARE was used as part of second-line therapy and 12.5 months OS when TARE was used as part of third-line or therapy or beyond. This partici-



**Figure 5:** Axial images in an 87-year-old woman diagnosed with colorectal carcinoma treated with left hemicolectomy in 2015. **(A, C)** Contrast-enhanced CT images show a 2.6-cm segment VII hepatic metastasis (oval in **A**), which did not respond to first-line chemotherapy using oxaliplatin. The participant was referred for arterial therapy and treated with 1.0 GBq to the segmental branch, as seen on the **(B)** SPECT image. Six months after treatment, the tumor measured 1.8 cm (oval in **C**), representing a partial response.



**Figure 6:** **(A–D)** Axial contrast-enhanced CT images in a 53-year-old man diagnosed with rectal carcinoma and treated with radiation and oxaliplatin-based chemotherapy in 2016. His cancer progressed after 2 months of therapy, developing liver metastases **(A)**, which stabilized with 5 months of irinotecan-based therapy **(B)**. He received 1.3 GBq to his right lobe in October 2016, with partial response identified at 2-month follow-up venous-phase CT **(C)**. Five months after treatment, he developed extrahepatic progressive disease **(D)** with a malignant left pleural effusion present at CT.

patient group had substantial disease: 28% of participants had 26% or greater hepatic tumor involvement, and 38% had extrahepatic disease. The study group was also heavily pretreated: 41% of participants had progressed on second-line therapy, 14% had previously undergone resection, and 10% had undergone multiple liver-focused interventions before

TARE. Despite these factors, the cohort had a 31% objective response rate and 68% disease control rate; these values approach those reported in the EPOCH (or Evaluating TheraSphere in Patients with Metastatic Colorectal Carcinoma of the Liver Who Have Progressed on First-Line Chemotherapy) study (with 34% and 79.5%, respectively) (8), in which all patients undergoing radioembolization received concomitant systemic therapy. The baseline tumor characteristics of this cohort more closely resembled those of the first-line SIRFLOX/FOXFIRE global study group (14), in which 32% of participants had more than 25% involvement and 36% had extrahepatic disease, compared with the group in EPOCH, in which 13.5% had more than 25% hepatic involvement and known extrahepatic disease was excluded from enrollment (8).

In our study, the longest OS was achieved in participants receiving TARE after progression on first-line treatment. The 17.4-month OS and 10.0-month PFS in this cohort are comparable with those of previous second-line studies, including EPOCH (14.0 months and 8.0 months, respectively). Second-line hepatic PFS in our study was 10.4 months, compared with 9.1 months in EPOCH. Although OS remains the primary



**Table 4: Grade 3 or Greater Toxicities**

Toxicity	Grade 3	Grade 4	Grade 5	Total
<b>Liver function</b>				
Albumin	13 (3.7)	0	0	13 (3.7)
Bilirubin	22 (6.3)	7 (2.0)	0	29 (8.4)
Aspartate transaminase	12 (3.5)	0	0	12 (3.5)
Alanine aminotransferase	6 (1.7)	0	0	6 (1.7)
International normalized ratio	3 (0.9)	0	0	3 (0.9)
Ascites	3 (0.9)	0	0	3 (0.9)
Hepatic encephalopathy	1 (0.2)	0	0	1 (0.2)
Hepatic failure	0	0	5 (1.4)	5 (1.4)
Subtotal*	60 (17)	7 (2.0)	5 (1.4)	72 (21)
<b>Other adverse events</b>				
Altered mental status	1 (0.2)	0	0	1 (0.2)
Cardiac chest pain	1 (0.2)	0	0	1 (0.2)
Death	0	0	0	0
Esophageal variceal hemorrhage	0	1 (0.2)	0	1 (0.2)
Gallbladder obstruction	1 (0.2)	0	0	1 (0.2)
Hepatic infection	1 (0.2)	0	0	1 (0.2)
Pain	1 (0.2)	0	0	1 (0.2)
Thrombocytopenia	0	1 (0.2)	0	1 (0.2)
Total*	65 (19)	9 (2.6)	5 (1.4)	79 (23)

Note.—Toxicity data were available for 347 participants. Data are numbers of participants, with percentages in parentheses.

\* Percentages may not add up to totals because of rounding.

metric of oncologic efficacy, the current PFS and hepatic PFS data have value because response rates with systemic options decrease after second-line treatments. The OS and PFS for participants undergoing TARE as part of first-line therapy were shorter in our study than in the SIRLFOX/FOXfire global trials, in which OS and PFS were 22.6 and 11.0 months, respectively (14). The shorter OS and PFS in our study likely reflect use of TARE without chemotherapy in the first line of therapy. Current guidelines do not recommend the use of TARE as part of first-line therapy.

TARE after the failure of second-line systemic therapy improves OS compared with best supportive care and when combined with fluorouracil versus chemotherapy alone (12,15). More recent reports of TARE for salvage therapy demonstrated a survival of 10.0–10.6 months, compared with 12.5 months in our study (5,16,17). Systemic chemotherapy options after second-line chemotherapy have shorter PFS and OS than earlier regimens (18). By comparison, trifluridine and tipiracil combined and regorafenib resulted in 7.1- and 6.4-month median OS, respectively, compared with 5.3- and 5.0-month median OS with best supportive care (6,7). Although the rate of grade 3 or greater toxicities increased in our study when TARE was used for salvage therapy compared with first- or second-line therapy, the overall incidence of grade 3 hepatic enzyme toxicity with TARE remained low at less than 10%. Comparatively, the incidence of grade 3 toxicities with trifluridine and tipiracil combined and regorafenib was 69% and 93%, respectively (6,7).

The 8.4% bilirubin and 3.7% albumin grade 3 or greater toxicities in our study were slightly less than in the 531-patient

report by Hickey et al (13% bilirubin and 8% albumin) using glass microspheres (5) and more than in the 606-patient publication by Kennedy et al (3% bilirubin) with resin microspheres (11). Before salvage therapy in our study, the grade 3 toxicity rates were 3.7% for bilirubin and 1.7% for albumin. The FOXfire global trial reported 0.8% grade 3 bilirubin and 0.9% grade 3 ascites toxicities when TARE was used as first-line treatment.

Our study has limitations. First, it was nonrandomized with open-label treatment. Second, screening failures were not tracked. Third, there was less than 100% data entry because of the observational nature of the study. The different imaging and laboratory assessment strategies at treatment sites also led to lower percentages of the entire cohort undergoing response and toxicity assessment at the 6-month time point. Fourth, a portion of the cohort had undergone previous hepatic interventions. Fifth, the identification of molecular targets to treat colorectal cancer evolved over the course of the

study, including the identification of shorter OS in the setting of right-sided primary tumors. These demographic points were not collected as a part of the registry.

In conclusion, transarterial radioembolization (TARE) with yttrium 90 microspheres resulted in 15.0-month overall survival (OS) in a cohort of 498 participants with metastatic colorectal cancer—specifically, 17.4 months when used as part of second-line treatment and 12.5 months as part of salvage therapy. Based on the current findings, future research options include initiating TARE combined with fluoropyrimidine therapy at the end of second-line chemotherapy in patients with liver-dominant metastases as intensification therapy versus fluoropyrimidine therapy alone. Additionally, further randomized controlled trials combining TARE with other agents in the salvage setting are merited to maximize survival options for patients with liver-dominant metastatic disease, with the goal of improving OS.

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