Original Article

Incidence and risk factors for sustained hepatic function toxicity 6 months after radioembolization: analysis of the radiation-emitting sir-spheres in non-resectable liver tumor (RESIN) registry

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Background: To quantify rates and risk factors for toxicity after hepatic radioembolization using resin yttrium-90 microspheres.

Methods: Radiation-Emitting SIR-Spheres in Non-resectable liver tumor (RESIN) registry enrollees were reviewed with 614 patients included. Mean patient age was 63.1±12.5 years. The majority of patients were male (n=375, 61%) and white (n=490, 80%). Common tumor types were hepatocellular (n=197, 32%), colorectal (n=187, 30%) and neuroendocrine (n=56, 9%). Hepatotoxicity was measured using the Common Terminology Criteria for Adverse Events (CTCAE v 5). Potential risk factors for hepatotoxicity were tested using the Kruskal-Wallis or Pearson Chi-squared tests, and multivariate linear regressions.

Results: At 6 months, 115 patients (18.7%) died (n=91, 14.8%), entered hospice (n=20, 3.3%) or sought treatment elsewhere (n=4, 4%). Seven (1.1%) deaths were from liver decompensation. Grade 3 toxicity rates were: bilirubin (n=85, 13.8%), albumin (n=28, 4.6%), ALT (n=26, 4.2%) and AST (n=37, 6.0%). For each of these liver function test components, baseline abnormal labs predicted Grade 3 toxicity at follow-up by Kruskal-Wallis test (P<0.001) and linear regression (all P<0.03). Other significant factors predicting toxicity at regression included elevated Body-Mass Index (albumin P=0.0056), whole liver treatment (bilirubin P=0.046), and lower tumor volume (ALT and INR, P<0.035 for both).

Conclusions: Baseline liver function abnormalities prior to radioembolization is the strongest predictor of post-treatment Grade 3 toxicity with rates as high as 13.8%. Toxicity rates for specific lab values are affected by large volume treatments especially with low tumor volumes.

Keywords: Radioembolization; brachytherapy; hepatocellular carcinoma (HCC); colorectal carcinoma; liver metastases

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Introduction

Transarterial radioembolization (TARE) is a component of many interventional oncology practices (1-3). Beyond, hepatocellular carcinoma (HCC) and neuroendocrine tumor, integration of radioembolization for other tumors into treatment guidelines has been challenging (4-7). A contributing factor to slow incorporation of TARE has been the failure to reach primary endpoints in all recent randomized prospective trials to treat colorectal carcinoma and HCC (8,9). With development of newer drugs and modalities to treat hepatic dominant tumors, combining TARE with other targeted therapies or following targeted external beam radiotherapy will need to be assessed with limited existing outcomes and toxicity data. Greater use in practice will require larger data sets, including expected toxicity profiles (2,10-14).

For patients with liver-dominant, but not isolated disease, integrating arterial treatment with other systemic, biologic, or immune therapies could result in improved patient outcomes, resulting in greater utilization of intra-arterial therapy (2,15). Patients with cirrhosis-related HCC or undergoing treatment with hepatotoxic drugs such as oxaliplatin or irinotecan may be at different risks of hepatotoxicity with TARE than other patients. However, a recent publication suggested toxicity development beyond 3 months in neuroendocrine tumors, a disease entity without either of the above characteristics (RECH) (16). An updated understanding of expected radioembolization-related hepatic toxicity will facilitate future combination trials. The resulting information could affect patient selection, dosimetry, and selection of potential agents to study in combination therapy.

The Radiation-Emitting SIR-spheres In Non-resectable liver tumor (RESIN) registry (NCT02685631) is a prospective observational study collecting data regarding dosimetry, response and toxicity for tumors treated with ceramic radioembolization emitting microspheres (Sirtex, Boston, MA, USA). Study sites include the spectrum of interventional radiology practices from academic centers to private practice groups, allowing a real-world evidence of device utilization in the United States. The primary purpose of the current review was to review data to quantify hepatic toxicity incidence 6 months after therapy with radioembolization and identify demographic and clinical factors which increased risk of significant toxicity of liver function. We present the study in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jgo-20-346).

Methods

Registry structure

The RESIN registry is an observational database. This study (GI 1523) was approved by the institutional review board at Vanderbilt University Medical Center (IRB #150407) and at the other sites. Informed consent was obtained from all patients at each center. The study was performed in keeping with the Declaration of Helsinki (as revised in 2013). As a real-world data collection, physicians at each site assessed patients for appropriateness for treatment, prescribed activity and ordered follow-up labs and imaging per local practice. Inclusion criteria were based on local decision-making and operator decision that TARE was an appropriate therapy. Patients had to be 18 years old or older and had to be capable of providing informed consent. No surrogate consent was allowed. Specific tumor sizes and laboratory thresholds were not used to determine eligibility in this data collection. At the time of data evaluation (March, 2020), 614 patients had demographic, prescription and treatment data entered along with 6-month imaging and/or laboratory follow-up data. This review tracks outcomes at 6 months after initial TARE treatment. Disease types with an incidence of less than 5 patients were designated as "other" and grouped together. Patients who received systemic therapy were divided into groups receiving one, two, or three or more lines of therapy. Patients were enrolled on the date of first radioembolization. The Society of Interventional Radiology Quality Improvement Guidelines were used for terminology (17).

Demographics

Baseline patient factors by tumor type are outlined in *Table 1*. Median and mean age was 65 and 63.1±12.5 years (range, 20–93 years). Three hundred seventy-five (61.1%) male, 238 female (38.8%) and 1 non-binary (0.2%) patients were treated. HCC (n=197), colorectal carcinoma (n=187), and neuroendocrine tumor (n=56) were the most common diagnoses. There were significant differences between tumor types in patient age and gender. The oldest patient group was cholangiocarcinoma (median 70; IQR 63.2–74.8). HCC had the most male patients for any tumor type (78%). Five hundred forty three patients (91%) were ECOG 0 (274, 46.0%) or 1 (269, 45.2%). Seven ECOG 3–4

Table 1 Group demographics. The number and percent of included data points are included in the right column. The Kruskal-Wallis Test (1 in final column) was used for continuous variables and Pearson Chi-squared test (2 in final column) for discrete variables

Variable	HCC	CRC	NET	Cholangio	Breast	Melanoma	Pancreas	Esophageal	Other	Cohort	Number reported	P value/test
Number	199	188	56	34	26	16	16	7	72		614	
Age (mean and IQR)	64 (60.0–70)	61 (53.0–69)	64.5 (48.2–69)	70 (63.2–74.8)	60 (53.2–68.8)	63.5 (48.2–69)	59 (57.8–63.5)	59 (55.5–64.5)	66 (59.8–71.2)	64 (56.0–70)	614 (100%)	<0.001*/1
Gender											614 (100%)	<0.001*/2
Female	44 (22%)	73 (39%)	28 (50%)	15 (44%)	26 (100%)	10 (62%)	7 (44%)	2 (29%)	35 (49%)	238 (38.7%)		
Male	155 (78%)	115 (61%)	28 (50%)	18 (53%)	0 (0%)	6 (38%)	9 (56%)	5 (71%)	37 (51%)	375 (61.1%)		
Non-binary	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.2%)		
Race											614 (100%)	0.96/2
White	151 (76%)	146 (78%)	45 (80%)	28 (82%)	22 (85%)	16 (100%)	15 (94%)	7 (100%)	60 (83%)	490 (79.8%)		
Black	23 (12%)	22 (12%)	6 (11%)	3 (9%)	4 (15%)	0 (0%)	0 (0%)	0 (0%)	6 (8%)	65 (10.6%)		
Asian	7 (4%)	4 (2%)	2 (4%)	3 (9%)	0 (0%)	0 (0%)	1 (6%)	0 (0%)	2 (3%)	19 (3.1%)		
American Indian/Alaskan	2 (1%)	4 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	5 (0.8%)		
Native Hawaiian	2 (1%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (0.5%)		
Other/unknown	14 (7%)	12 (7%)	2 (4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (5%)	32 (5.2%)		
Ethnicity											614 (100%)	0.96/2
Hispanic or Latino	11 (6%)	12 (6%)	2 (4%)	2 (6%)	2 (8%)	0 (0%)	1 (6%)	0 (0%)	3 (4%)	32 (5.2%)		
Non-Hispanic	171 (86%)	164 (87%)	51 (91%)	31 (91%)	21 (81%)	16 (100%)	15 (94%)	7 (100%)	65 (90%)	542 (88.3%)		
Other/unknown	17 (9%)	12 (7%)	3 (5%)	1 (3%)	3 (12%)	0 (0%)	0 (0%)	0 (0%)	4 (6%)	40 (6.5%)		
ECOG											594 (96.9%)	0.88/2
0	93 (49%)	80 (44%)	24 (44%)	21 (66%)	9 (36%)	7 (44%)	6 (43%)	2 (29%)	31 (43%)	274 (46%)		
1	79 (42%)	89 (49%)	26 (47%)	8 (25%)	15 (60%)	8 (50%)	8 (57%)	4 (57%)	32 (44%)	269 (45.2%)		

Table 1 (*continued*)

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Table 1 (*continued*)

Variable	HCC	CRC	NET	Cholangio	Breast	Melanoma	Pancreas	Esophageal	Other	Cohort	Number reported	P value/test
2	13 (7%)	12 (7%)	5 (9%)	3 (9%)	1 (4%)	1 (6%)	0 (0%)	1 (14%)	9 (12%)	45 (7.6%)		
3	3 (2%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)	0 (0%)	5 (0.8%)		
4	2 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (0.3%)		
Portal vein											601 (97.8%)	0.001*/2
Patent	162 (84%)	169 (92%)	49 (88%)	29 (91%)	24 (93%)	16 (100%)	12 (80%)	6 (86%)	65 (90%)	532 (92.5%)		
Segmental thrombus	10 (5%)	1 (1%)	1 (2%)	2 (6%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)	1 (2%)	16 (2.8%)		
Lobar thrombus	8 (4%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	10 (1.7%)		
Main thrombus	10 (5%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	11 (1.9%)		
Cavernous transformation	4 (2%)	0 (0%)	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)	1 (2%)	6 (1.0%)		
Not provided	0 (0%)	13 (7%)	5 (9%)	0 (0%)	2 (7%)	0 (0%)	2 (14%)	1 (14%)	5 (7%)			
Tumor volume (median and IQR)	10.1% (5–25)	18.1% (5.5–30)	22% (9–39.9)	15.5% (7.6–30)	18.5% (9.3–40)	7% (4.6–22.3)	17% (9–28.8)	19% (7.5–38.3)	15% (7.5–30)	15% (6.9–30%)	567 (92.3%)	0.14/1
Treatment area											614 (100%)	<0.001*/2
Whole	51 (26%)	101 (54%)	33 (59%)	13 (38%)	16 (62%)	7 (44%)	11 (69%)	3 (43%)	33 (46%)	270 (44%)		
Right	93 (47%)	37 (39%)	19 (34%)	16 (47%)	5 (19%)	5 (31%)	4 (25%)	3 (43%)	31 (43%)	243 (39.6%)		
Left	36 (18%)	14 (7%)	4 (7%)	2 (6%)	5 (19%)	2 (12%)	1 (6%)	1 (14%)	4 (6%)	68 (11.1%)		
Segmental	17 (9%)	2 (1%)	0 (0%)	2 (6%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)	3 (4%)	23 (3.7%)		
Lobe + segment	2 (1%)	2 (1%)	0 (0%)	1 (3%)	0 (0%)	1 (6%)	0 (0%)	0 (0%)	1 (1%)	10 (1.6%)		
Delivered activity (median and IQR in GBq)	1.3 (0.9–1.7)	1.5 (1.1–2.0)	1.6 (1–1.9)	1.5 (1.1–1.7)	1.5 (1.1–1.9)	1.3 (0.9–1.7)	1.6 (1.4–1.8)	1.8 (1.4–2.6)	1.4 (1.1–1.9)	1.3 (0.9–1.7)	614 (100%)	0.004*/1
BMI (median and IQR	27.7 (24.5–32.6)	27.7 (24–31.6)	26.8 (23.3–33.5)	26.9 (24.3–30.5)	27.7 (24–33.1)	23.8 (22.4–27.8)	29.1 (23.1–32.7)	27.5 (25.6–28.6)	27.6 (23.6–30.9)	27.53 (23.9–31.6)	609 (99.2%)	0.43/1

*, P<0.05. HCC, hepatocellular carcinoma; CRC, colorectal carcinoma; NET, neuroendocrine tumor; ECOG, Eastern Cooperative Oncology Group; SBRT, stereotactic body radiotherapy; GBq, gigabecquerel; BMI, body-mass index; IQR, interquartile range.

Table 2 Treatments prior to radioembolization by tumor type

Pathology	Total (N patients)	Surgery	Chemo 1 line	Chemo 2 lines	Chemo 3+ lines	Ablation	SBRT	Arterial
Hepatocellular	197	8, 4.1%	28, 14.2%	20, 10.2%	8, 4.1%	24, 12.2%	2, 1.0%	50, 25.4%
Colorectal	187	29, 15.5%	35, 18.7%	43, 23.0%	61, 32.6%	26, 13.9%	12, 6.4%	14, 7.5%
Neuroendocrine	56	8, 14.3%	20, 35.7%	9, 16.1%	14, 25%	4, 7.1%	3, 5.4%	9, 16.1%
Cholangiocarcinoma	35	3, 8.6%	11, 31.4%	6, 17.1%	5, 14.3%	2, 5.7%	4, 11.4%	4, 11.4%
Breast	27	1, 3.7%	1, 3.7%	3, 11.1%	15, 55.6%	2, 7.4%	1, 3.7%	3, 11.1%
Melanoma	16	0, 0%	6, 37.5%	4, 25%	2, 12.5%	1, 6.3%	1, 6.3%	1, 6.3%
Pancreatic	16	2, 12.5%	4, 25%	4, 25%	4, 25%	0, 0%	2, 12.5%	1, 6.3%
Esophageal	7	0, 0%	1, 14.3%	2, 28.6%	4, 57.1%	0, 0%	1, 14.3%	0, 0%
Other	73	8, 11.0%	20, 27.4%	17, 23.3%	27, 37%	5, 6.8%	7, 9.6%	4, 5.5%
Total	614, 100.0%	59, 9.6%	126, 20.5%	108, 17.6%	140, 22.8%	64, 10.4%,	27, 5.1%	86, 14.0%

Chemo, systemic therapy; SBRT, stereotactic body radiation to hepatic malignancy; Arterial, previous embolization or chemoembolization.

(1.1%) patients were treated after clinical assessment. Five of these patients had HCC and 2 had colorectal carcinoma. Portal vein thrombosis was most common in the HCC group. Twenty-eight HCC patients (14%) had segmental (n=10;5%), lobar (n=8, 4%), or main (n=10, 5%) portal vein thrombosis. Median and mean delivered activity was 1.4 and 1.5±0.7 gigabecquerels (GBq). Investigators used quantitative tools to assess tumor burden in 331 patients (58%) and visual assessment in the remainder. Whole-liver treatment was the most common approach, in 270 (44%) of patients. Infusion of a lobe plus an additional segment was the least common approach (n=10, 1.6%). The median prescribed activity by treatment area was: whole liver: 1.9 GBq (IQR: 1.6–2.2 GBq), right lobe 1.2 GBq (IQR 1–1.5 GBq), left lobe: 0.8 GBq (IQR: 0.6–1 GBq), SEGmental: 0.9 GBq (0.4–1.1 GBq), lobe plus segment: 1.3 Gbq (1–1.5 GBq).

Treatments prior to TARE are outlined by tumor type in *Table 2*. The most common treatments prior to TARE was systemic therapy (n=374, 60.9%). In this review, systemic therapy accounts for any treatment prescribed by a medical oncologist including chemo-, biologic and immunotherapies. For patients who received systemic therapy, the average number of treatment lines prior to radioembolization was 2.3. One hundred forty (22.8%) patients received three or more lines of systemic therapy, including 61 (32.6%) colorectal cancer and 15 (55.6%) breast cancer patients. Fifty-five (10%) patients underwent resection, most commonly for colorectal carcinoma (n=29, 15.5%) and neuroendocrine tumor (n=8, 14.3%). Regarding locoregional therapies, arterial embolization was the most common. Eighty-five patients (14%) underwent chemoembolization or embolization, most commonly in patients with HCC (n=50, 25.4%), and neuroendocrine tumor (n=9, 16.1%).

Follow-up

Lab and imaging follow-up were performed per institutional preferences with data collected at 6-month intervals. Quantifiable toxicities of liver function were assessed using serum bilirubin, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and international normalized ratio (INR) with toxicity defined using common terminology criteria for adverse events (CTCAE) version 5. Additionally, absolute neutrophil count was assessed at 6 months. Patients who left the study were censored at the date of removal. The presence and grading of baseline lab abnormalities was defined using values previously used in CTCAE v4 including bilirubin >1.8 mg/dL (n=89, 14.5%), albumin <3 g/dL (n=391, 63.7%), ALT >450 U/L (n=174, 28.3%), AST >450 U/L (n=200, 32.6%), and INR >1.8 (n=19, 3.1) for patients not on anticoagulation. Additional treatments in the 6-month window after TARE were tracked. Final toxicity assessment was performed at 6 months ±2 weeks or when censored. Toxicities were calculated using CTCAE v5. Sustained toxicity was defined as Grade 3 or greater toxicity presence at 6 months. Imaging response at 6 months was determined with response criteria in solid tumors (RECIST) or modified RECIST based on

baseline enhancement characteristics at 6 months ±2 weeks or when censored. Objective response was defined as the sum of complete and partial response. Disease control was defined as objective response plus stable disease.

Statistical analysis

Demographic factors were assessed separately for association with clinical toxicity by grade using the Kruskal-Wallis Test for continuous variables and Pearson Chi-squared test for discrete variables. Multivariable linear regressions were performed for the different post-treatment liver functions to evaluate contributing baseline factors for each different measure of hepatic function to significant toxicity. Finally, for the most common tumor types, multivariable linear regression was performed to identify specific baseline factors by pathologic entity. For all analyses, a P value of <0.05 was considered statistically significant. Calculations were performed using R Version 3.6.2 (Vienna, Austria).

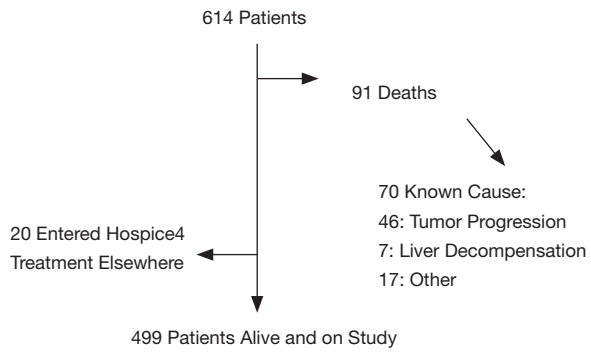

Figure 1 Flow diagram of study participants at 6 months.

Results

Drop-out

One hundred fifteen patients (18.7%) patients dropped off the study at a mean of 112±36 days (*Figure 1*). Ninety-one (79% of the drop-out group) patients died, 20 (17%) entered hospice and four (4%) sought treatment elsewhere. The cause of death was documented in 70 (77%) patients of the 91 who expired. In this subgroup, 46 patients (66%) died from tumor progression, and 7 (10%) died from liver decompensation without evidence of tumor progression. The remaining patients died of other causes. The overall liver decompensation rate was 7/115 (6.1%) for all patients dropping off the study and was 7/614 (1.1%) for the entire cohort.

Additional treatments

Table 3 reviews additional treatments that were given in the 6 months after TARE. One-third of patients (205/614, 33.4%) had any type of additional treatment. Chemotherapy was the most common treatment, given to 129 patients (21%) of the group. Twenty-six of the 45 (58%) patients with colorectal cancer received 3rd line therapy or beyond. Arterial therapy was used in 15% of patients with HCC, but

Table 3 Treatments in the first 6 months after radioembolization

Pathology	Total (N patients)	Surgery	Chemo	Ablation	SBRT	Arterial
Hepatocellular	86/197 (44%)	7 (3.6%)	36 (21.8%)	9 (4.6%)	4 (2%)	30 (15.2%)
Colorectal	58/187 (31.0%)	3 (1.6%)	45 (24%)	7 (3.7%)	2 (1%)	1 (0.5%)
Neuroendocrine	9/56 (16.1%)	0 (0%)	7 (12.5%)	0 (0%)	0 (0%)	2 (3.6%)
Cholangiocarcinoma	11/35 (31.4%)	1 (2.9%)	7 (20%)	0 (0%)	2 (5.7%)	1 (2.9%)
Breast	6/27 (22.2%)	0 (0%)	4 (14.8%)	1 (3.7%)	1 (3.7%)	0 (0%)
Melanoma	4/16 (25%)	0 (0%)	3 (18.8%)	0 (0%)	0 (0%)	1 (6.3%)
Pancreatic	5/16 (31.2%)	0 (0%)	3 (6.3%)	0 (0%)	0 (0%)	2 (12.5%)
Esophageal	2/7 (28.6%)	0 (0%)	2 (28.6%)	0 (0%)	0 (0%)	0 (0%)
Other	24/73 (32.9%)	0 (0%)	22 (30.1%)	0 (0%)	0 (0%)	2 (2.7%)
Total	205/614 (33.4%)	11 (1.8%)	129 (21%)	17 (2.8%)	9 (1.5%)	39 (6.4%)

Chemo, systemic therapy; SBRT, stereotactic body radiation to hepatic malignancy; Arterial, embolization or chemoembolization.

Table 4 Toxicity at 6 months after radioembolization

Tumor	n	Bilirubin		Albumin		ALT		AST		INR	
		Gr 1–2	Gr 3+	Gr 1–2	Gr 3	Gr 1–2	Gr 3+	Gr 1–2	Gr 3+	Gr 1–2	Gr 3
Colorectal	187	44 (23.5%)	28 (15%)	80 (42.8%)	10 (5.3%)	80 (42.8%)	4 (2.1%)	102 (54.5%)	8 (4.3%)	20 (10.7%)	5 (2.7%)
Hepatocellular	197	89 (45.2%)	34 (17.3%)	103 (52.3%)	10 (5.1%)	65 (33%)	11 (5.6%)	87 (44.2%)	8 (4.1%)	39 (19.8%)	0 (0%)
Neuroendocrine	56	5 (8.9%)	2 (3.6%)	12 (21.4%)	2 (3.6%)	15 (26.8%)	2 (3.6%)	22 (39.3%)	3 (5.4%)	1 (1.8%)	0 (0%)
Cholangiocarcinoma	35	4 (11.4%)	3 (8.6%)	12 (34.3%)	1 (2.9%)	10 (28.6%)	0 (0%)	11 (31.4%)	1 (2.9%)	0 (0%)	0 (0%)
Breast	27	6 (22.2%)	2 (7.4%)	11 (40.1%)	1 (3.7%)	13 (48.1%)	1 (3.7%)	14 (51.9%)	4 (14.8%)	2 (7.4%)	0 (0%)
Melanoma	16	1 (6.2%)	3 (18.8%)	6 (37.5%)	0 (0%)	7 (43.8%)	0 (0%)	8 (50%)	1 (6.2%)	2 (12.5%)	0 (0%)
Pancreatic	16	3 (18.8%)	2 (12.5%)	7 (43.8%)	0 (0%)	7 (43.8%)	0 (0%)	8 (50%)	0 (0%)	3 (18.8%)	0 (0%)
Esophageal	7	3 (42.9%)	2 (28.6%)	5 (71.4%)	1 (14.3%)	3 (42.9%)	1 (14.3%)	4 (57.1%)	2 (28.6%)	1 (14.3%)	1 (14.3%)
Other	73	16 (21.9%)	9 (12.3%)	29 (39.7%)	3 (4.1%)	27 (36.9%)	7 (9.6%)	35 (47.9%)	10 (13.7%)	7 (9.6%)	1 (1.4%)
Total	614	171 (27.9%)	85 (13.8%)	265 (43.2%)	28 (4.6%)	227 (37%)	26 (4.2%)	291 (47.4%)	37 (6%)	75 (12.2%)	7 (1.1%)

Gr, grade; ALT, alanine aminotransferase; AST, aspartate transaminase; INR, international normalized ratio.

only in 2% of the remaining patients. Surgery, ablation and stereotactic radiation were each used in less than 3% of the cohort.

Liver-function toxicity

Table 4 demonstrates 6-month toxicity including the final labs for patients who dropped out. Grade 3 bilirubin toxicities were identified in 13.8% of patients. Both HCC (17.3%) and colorectal carcinoma (15%) had grade 3 toxicity rates that exceeded this value. Grade 3 albumin toxicities were 4.6%, again with a greater incidence in HCC (5.3%) and colorectal carcinoma (5.1%). Grade 3 ALT and AST toxicities were 4.2% and 6%, respectively. Grade 3 INR toxicity occurred in 7 patients (1.1%) within the cohort. Five of these 7 (71.4%) patients had colorectal carcinoma. The median absolute neutrophil count at 6 months was 4,300 (IQR: 3,100–6,530). Fourteen patients (2.2%) developed an absolute neutrophil count <1,500 at 6 months. No patients had an absolute neutrophil count of 500 or less. There was no statistical difference in development of significant hepatic function toxicity based on the method of dosimetry.

Other toxicity

Other grade 3–5 toxicities are reported in *Table 5*. Thirty-one grade 3, nine grade 4 and 2 grade 5 events were reported. The most commonly reported toxicities were thrombocytopenia in 8 patients (1.3%) and abdominal pain in 6 patients (1.0%). Two patients (0.3%) developed gastric ulcers.

Response

At 6 months, 499 (81.2%) patients of the original group were available for imaging follow-up. Of these patients, 483 (78.7%) had imaging within the defined response assessment time which used mRECIST or RECIST to determine response. The remaining patients (n=16, 2.6%) had positron emission scanning with or without computed tomography. Thirty-two (6.6%) of the evaluable patients had complete response, 143 (29.6%) had partial response, 150 (31.1%) had stable disease and 158 (32.5%) had progressive disease. One hundred seventy-five (36.2%) of patients had an objective response, and 325 (67.3%) of patients had disease control. Of the three most common tumor types, neuroendocrine tumor had the highest rates of objective

Table 5 Other grade 3 and greater toxicities

Variable	Grade 3	Grade 4	Grade 5
Abdominal distension	2	0	0
Abdominal infection	1	0	0
Abdominal pain	6	0	0
Alkaline phosphatase increased	1	0	0
Ascites	1	0	0
Encephalopathy	1	0	0
Esophageal varices hemorrhage	0	1	0
Fatigue	1	0	0
Fever	1	0	0
Flank pain	1	0	0
Gallbladder obstruction	1	0	0
Gastric ulcer	1	1	0
Generalized muscle weakness	1	0	0
Hepatobiliary disorders: other, specify	1	0	0
Hyperglycemia	0	1	0
Ileus	1	0	0
Lymphocyte count decreased	2	0	0
Nausea	1	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	1
Pancreatitis	1	0	0
Platelet count decreased	3	5	0
Renal and urinary disorders: other	0	1	0
Scrotal pain	1	0	0
Stomach pain	1	0	0
Other	2	0	1
Total	31	9	2

response (61.4%) and disease control (93.2%), while HCC had the greatest percentage of complete responses (16.5%). One hundred forty-eight patients (93.6%) with progressive disease developed hepatic progression. Of this group, 111 (75%) progressed in the treatment zone while 37 (25%) progressed outside the previously treated area. Additionally, 94 patients with progressive disease (59%) developed new extrahepatic disease.

Predictive factors of group toxicity

Several factors predicted grade 3 or greater toxicity (*Table 6*) including increased age (P=0.046), male gender (P<0.001), primary liver cancer (P<0.001), metastatic tumor type (P<0.001), increased lung shunt percentage (P=0.004), increased delivered activity (P=0.04), bilobar compared with unilobar tumor (P=0.04), and baseline laboratory elevation compared with normal labs (P<0.001). Undergoing previous liver tumor intervention was associated with significant toxicity as well compared to treatment naïve patients (P=0.05). Previous surgery (P=0.01) specifically predicted an adverse outcome.

At linear regression, baseline liver function toxicity (t=16.6, P<0.0001) and increased BMI (t=2.79, P=0.0056)

Table 6 Association of baseline factors with hepatic toxicity. The number and percent of included data points are included in the right column. The Kruskal-Wallis Test (1 in final column) was used for continuous variables and Pearson Chi-squared test (2 in final column) for discrete variables

Variable	N	No toxicity, N=337	Grade 1, N=88	Grade 2, N=83	Grade 3, N=66	Grade 4, N=19	Combined, N=614	P value/test
Age	614	64 (55.0–70)	64.5 (60.0–70)	67 (59.5–71)	62.0 (56–67.8)	59 (55.5–68)	64 (56.0–70)	0.046*/1
Gender	614							<0.001*/2
Female		158 (47%)	18 (20%)	24 (29%)	23 (35%)	7 (37%)	230	
Male		178 (53%)	70 (80%)	59 (71%)	43 (65%)	12 (63%)	362	
Non-binary		1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1	
Race	614							0.66/2
White		264 (78%)	63 (72%)	72 (87%)	54 (82%)	18 (95%)	471 (79%)	
Black		39 (12%)	10 (11%)	7 (8%)	6 (9%)	0 (0%)	62 (10%)	
Asian		11 (3%)	5 (6%)	1 (1%)	2 (3%)	0 (0%)	19 (3%)	
American Indian/Alaska		4 (1%)	1 (1%)	0 (0%)	1 (2%)	0 (0%)	6 (1%)	
Native Hawaiian		2 (1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	3 (1%)	
Other/unknown		17 (5%)	8 (9%)	3 (3%)	3 (5%)	1 (5%)	32 (6%)	
Ethnicity	614							0.18/2
Hispanic or Latino		19 (6%)	1 (1%)	3 (4%)	6 (9%)	2 (11%)	31 (5%)	
Non-Hispanic		298 (88%)	76 (86%)	75 (90%)	56 (85%)	17 (89%)	522 (88%)	
Other/unknown		20 (6%)	11 (12%)	5 (6%)	4 (6%)	0 (0%)	40 (7%)	
Tumor type	614							<0.001*/2
Primary		101 (30%)	56 (64%)	39 (47%)	33 (50%)	5 (26%)	234 (39%)	
Metastatic		236 (70%)	32 (36%)	44 (53%)	33 (50%)	14 (74%)	359 (61%)	
Primary tumor	239							0.007*/2
HCC		73 (72%)	52 (93%)	37 (95%)	29 (88%)	5 (100%)	196 (84%)	
Cholangio		26 (26%)	3 (5%)	1 (3%)	3 (9%)	0 (0%)	33 (14%)	
Other		2 (2%)	1 (2%)	1 (3%)	1 (3%)	0 (0%)	2 (2%)	
All tumors	614							<0.001*/2
HCC		73 (22%)	52 (59%)	37 (45%)	29 (44%)	5 (26%)	196 (33%)	
Colorectal		107 (32%)	14 (16%)	30 (36%)	20 (30%)	8 (42%)	179 (30%)	
Neuroendocrine		46 (14%)	4 (5%)	1 (1%)	2 (3%)	0 (0%)	53 (9%)	
Cholangio		26 (8%)	3 (3%)	1 (1%)	3 (5%)	0 (0%)	33 (6%)	
Breast		18 (5%)	3 (3%)	3 (4%)	1 (2%)	1 (5%)	26 (4%)	
Melanoma		12 (4%)	1 (1%)	0 (0%)	1 (2%)	2 (11%)	16 (3%)	
Pancreas		8 (2%)	2 (2%)	1 (1%)	1 (2%)	1 (5%)	13 (2%)	
Esophageal		2 (1%)	1 (1%)	2 (2%)	2 (3%)	0 (0%)	7 (1%)	
Lung		5 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	6 (1%)	

Table 6 (*continued*)

Table 6 (*continued*)

Variable	N	No toxicity, N=337	Grade 1, N=88	Grade 2, N=83	Grade 3, N=66	Grade 4, N=19	Combined, N=614	P value/test
Other		40 (12%)	8 (9%)	7 (8%)	7 (11%)	0 (0%)	62 (10%)	
ECOG	594							0.13/2
0		152 (47%)	38 (45%)	44 (54%)	22 (34%)	6 (35%)	262 (46%)	
1		144 (44%)	38 (45%)	30 (37%)	37 (58%)	11 (65%)	260 (45%)	
2		26 (8%)	6 (7%)	8 (10%)	4 (6%)	0 (0%)	44 (8%)	
3		2 (1%)	3 (4%)	0 (0%)	0 (0%)	0 (0%)	5 (1%)	
4		1 (<1%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)	2 (<1%)	
BMI	609	27.6 (23.8–32)	27.2 (23.1–30.1)	27.3 (23.4–31.4)	27.7 (24.7–31.4)	28.5 (25.1–30.3)	27.6 (23.0–31.6)	0.78/1
Lung shunt %	610	4% (2.7–6.1)	5% (3.2–7)	4.8% (3.3–7.3)	5.6% (3–8.9)	5.8% (4.1–7.5)	4.4% (2.9–6.8)	0.004*/1
Portal vein	601							0.075/2
Patent		299 (90%)	74 (86%)	73 (89%)	55 (85%)	14 (82%)	515 (89%)	
Segmental thrombus		9 (3%)	4 (5%)	1 (1%)	1 (2%)	1 (6%)	16 (3%)	
Main thrombus		2 (1%)	3 (3%)	4 (5%)	2 (3%)	0 (0%)	11 (2%)	
Lobar thrombus		4 (1%)	2 (2%)	1 (1%)	2 (3%)	0 (0%)	9 (2%)	
Cavernous transformation		1 (<1%)	1 (1%)	0 (0%)	3 (5%)	1 (6%)	6 (1%)	
Tumor volume (%)	567	14.8% (5.5–30)	10% (6.0–25)	15% (6.5–25)	20% (9.3–30)	21.1% (9.9–30)	15% (6.9–30)	0.27/1
Prescribed activity (GBq)	614	1.4 (0.98–1.8)	1.3 (0.95–1.8)	1.4 (1.0–1.9)	1.6 (1.2–2.0)	1.5 (1.2–2)	1.4 (1.0–1.9)	0.037*/1
Measurement method	583							
Quantitative		188 (59%)	53 (64%)	44 (56%)	36 (58%)	10 (56%)	331 (58%)	0.85/2
Visual estimate		132 (41%)	30 (36%)	35 (44%)	26 (42%)	8 (44%)	231 (42%)	
Dosimetry method	356							0.5/2
BSA		105 (53%)	35 (56%)	32 (60%)	16 (59%)	3 (27%)	191 (54%)	
Empiric		1 (1%)	2 (3%)	2 (4%)	0 (0%)	0 (0%)	5 (1%)	
Modified BSA		56 (28%)	15 (24%)	14 (26%)	9 (33%)	4 (36%)	98 (28%)	
Partition		15 (8%)	6 (10%)	2 (4%)	1 (4%)	2 (18%)	26 (7%)	
Other		21 (11%)	4 (6%)	3 (6%)	1 (4%)	2 (18%)	31 (9%)	
Infusion zone	614							0.086/2
Whole liver		147 (44%)	30 (34%)	29 (35%)	37 (56%)	11 (58%)	254 (43%)	
Right		132 (39%)	41 (47%)	40 (48%)	21 (32%)	6 (32%)	240 (40%)	
Left		40 (12%)	9 (10%)	10 (12%)	6 (9%)	2 (11%)	67 (11%)	
Segment		12 (4%)	7 (8%)	4 (5%)	0 (0%)	0 (0%)	23 (4%)	
Lobe + segment		6 (1%)	1 (1%)	0 (0%)	2 (3%)	0 (0%)	9 (2%)	

Table 6 (*continued*)

Table 6 (*continued*)

Variable	N	No toxicity, N=337	Grade 1, N=88	Grade 2, N=83	Grade 3, N=66	Grade 4, N=19	Combined, N=614	P value/test
Baseline lab toxicity	614							<0.001*/1
Albumin		4.0 (3.7–4.2)	3.7 (3.5–4)	3.5 (3.1–3.8)	3.3 (2.7–3.6)		3.4 (3.8–4.1)	
Bilirubin		0.5 (0.4–0.7)	0.9 (0.6–1.2)	1.0 (0.6–1.3)	0.8 (0.5–1.1)	0.8 (0.6–1.2)	0.7 (0.5–0.9)	
ALT		23 (16.5–32.5)	36 (25.0–54)	48 (26.0–67)	29 (23.0–74)		30 (20.0–46)	
AST		26 (19.0–35)	37 (27.0–55)	46 (29.0–63)	72 (33.0–115)		35 (24.0–52)	
INR		1.1 (1–1.2)	1.2 (1.1–1.3)	1.3 (1.2–1.4)	1.1 (1.0–1.2)		1.1 (1.0–1.2)	
MELD (HCC only)	196	7 (7.0–9)	9 (7.5–12)_	11 (8.0–12)	9 (7.3–11)	13 (11–13.5)	8.5 (7.0–11)	<0.001*/1
Child Pugh (HCC only)	173	5 (5.0–6)	6 (5.0–7)	7 (6.0–7)	6 (5.3–7)	7 (6–7.5)	6 (5.0–7)	<0.001*/1
Imaging response	554							0.32/1
Complete response		16 (7%)	5 (6%)	5 (7%)	4 (7%)	1 (7%)	31 (6%)	
Partial response		87 (28%)	25 (32%)	17 (24%)	9 (15%)	2 (13%)	140 (26%)	
Stable disease		83 (27%)	20 (25%)	13 (18%)	24 (39%)	5 (33%)	145 (27%)	
Progressive disease		91 (29%)	18 (23%)	27 (38%)	14 (23%)	6 (40%)	156 (29%)	
Unevaluable		34 (11%)	11 (14%)	10 (14%)	10 (16%)	1 (7%)	66 (12%)	
Previous surgery	575							0.01*/2
Yes		40 (12%)	2 (2%)	5 (6%)	4 (7%)	4 (24%)	55 (10%)	
No		291 (88%)	86 (98%)	75 (94%)	55 (93%)	13 (76%)	536 (90%)	
Ablation	584							0.11/2
Yes		28 (8%)	9 (10%)	11 (13%)	8 (12%)	5 (26%)	61 (10%)	
No		303 (92%)	77 (90%)	72 (87%)	57 (88%)	14 (74%)	523 (90%)	
Embolization	583							0.25/2
Yes		39 (12%)	18 (20%)	14 (17%)	11 (17%)	3 (16%)	85 (15%)	
No		292 (88%)	70 (80%)	68 (83%)	52 (83%)	16 (84%)	498 (85%)	
External radiation	586							0.55/2
Yes		23 (7%)	2 (2%)	4 (5%)	3 (5%)	1 (5%)	33 (6%)	
No		310 (93%)	85 (98%)	78 (95%)	62 (95%)	18 (95%)	553 (94%)	
Lines systemic therapy	374	2 [1–3]	1 [1–2]	2 [1–4]	2 [1–4]		2 [1–3]	0.4/2

Items including ranges represent the median with lower and upper quartiles in parentheses. The number of reported outcomes from the entire patient group are included in the second column. *, P<0.05. HCC, hepatocellular carcinoma; ECOG, Eastern Cooperative Oncology Group; BMI, body-mass index; ALT, alanine aminotransferase; AST, aspartate transaminase; INR, international normalized ratio; Cholangio, cholangiocarcinoma; MELD, model for end-stage liver disease.

predicted post-therapy toxicity for albumin (*Table 7*). Baseline liver function elevation (t=3.7, P=0.0002) and whole liver therapy (t=2, P=0.05) predicted grade 3 toxicity for bilirubin (*Table 8*). The significant linear regression results for ALT, AST and INR are summarized in *Table 9*. Notably, baseline liver function toxicity was a strong predictor of grade 3 toxicity for ALT and AST.

Predictive Factors for the Most Common Tumors: The regression model fit for HCC (*Table 10*) and colorectal cancer (*Table 11*). Factors predicting any Grade 3 toxicity for HCC included presence of extrahepatic disease at treatment with TARE. Numerous factors predicted Grade 3 toxicity for colorectal carcinoma, including previous arterial intervention, lower prescribed activity, white race, increased BMI, presence of baseline toxicity, whole-liver therapy, and lower tumor volume.

Discussion

The current study found that abnormal baseline function tests were the single strongest predictor of grade 3 toxicity 6 months following radioembolization. This factor correlated with grade 3 elevations of bilirubin (n=85, 13.8%) and albumin (n=28, 4.6%). Other factors, such as elevated BMI, tumor volume, or whole-liver therapy predicted post-treatment toxicity of individual lab values. However, baseline liver toxicity applied universally across this patient sample outside of INR, which had the lowest incidence of grade 3 toxicity. This group was heavily pre-treated prior to radioembolization: 40.4% of the patients received 2 or more lines of systemic therapy, 9.6% underwent resection, and 29.5% had locoregional therapies including embolization, thermal ablation or SBRT. Most patients were treated as salvage candidates: 37.6% of HCC patients had previous arterial therapy/ablation and 28.3% had gotten systemic therapy, while 32.6% of colorectal and 25% of neuroendocrine patients had received 3 or more lines of therapy at the time of referral. The lack of additional therapy in two-thirds of the patient group reinforces the end-stage nature of the treatment group, particularly given the use of maintenance systemic agents for the majority of disease types outside of neuroendocrine tumor and HCC. Despite the extensive pre-treatment and salvage status, we achieved a 36% objective response and 67% disease control rate.

Both colorectal carcinoma and HCC had Grade 3 toxicity rates above the group mean for several lab values. This finding reflects baseline hepatotoxicity from previous chemotherapy used for colorectal carcinoma and underlying cirrhosis in HCC (18-20). The 1.1% incidence of likely radiation-induced liver disease (7/614 patients) is slightly lower than the 4% rate described by Kennedy *et al.* (13). The data in this patient group also reinforces findings from smaller studies including that patients with lower tumor burden have an increased risk of toxicity due to a greater proportion of activity delivery to uninvolved liver (21,22). Additionally, patients who have undergone previous resection are at increased risk of toxicity as dose calculations do not accommodate for smaller organs (1). Patients with colorectal cancer had the highest resection rate in our cohort.

Grade 3 bilirubin toxicities following radioembolization range from 5–13% for breast, hepatocellular and colorectal carcinoma and up to 21% following TACE (3,22-25). Hypoalbuminemia outcomes are reported as albumin toxicity or ascites development in different studies. Reported rates of grade 3 albumin toxicity range from 5-8% for radioembolization and 0–19% for TACE for HCC (3,22,23). Increased ascites following radioembolization has been reported in 5.1% of colorectal cancer patients and 29% of breast cancer patients following radioembolization (24-26). While not all systemic therapies are hepatotoxic, it is important for the treating interventional radiologist to recognize the increased risk when patients have received such agents in combination with baseline hepatic dysfunction. Pre-existing hepatic toxicity can be exacerbated after bilobar treatments.

HCC specific outcomes

The 197 patients with HCC had a broad range of treatment prior to TARE, including embolization in 50 (25.4%), ablation in 24 (12.2%), and systemic therapy in 28 (14.2%) patients. Previous resection was performed in 8 (4.1%) patients. Twenty-eight (14%) of patients had some degree of portal vein thrombosis including 10 (5%) with main portal vein occlusion. In this cohort, patients with primary tumors had greater baseline lab abnormalities. Seventeen patients (9%) were treated with segmental TARE, with the remaining getting whole liver (n=51, 26%) or lobar (n=129, 65%) infusion. The toxicity rate increased with elevated MELD and Child-Pugh scores. Significant bilirubin and albumin toxicity developed in 34 (17.3%) and 10 (5.1%) of patients, respectively. In the whole group linear regression, Bilirubin and albumin toxicity was also associated with bilobar therapy (P=0.046) and elevated BMI (P=0.0056).

Table 7 Linear regression of predicting demographics for grade 3 albumin toxicity

Variable	Coefficient	Standard error	*t*	Prob (> l t l)
Intercept	0.20	0.29	0.68	0.50
Age	–0.0015	0.0023	–0.64	0.52
Gender (male)	0.053	0.053	1.01	0.31
Race (Black *vs*. other)	0.13	0.12	1.11	0.27
Race (White *vs*. other)	–0.28	0.091	–0.31	0.76
Cancer type (metastatic *vs*. other)	–0.03	0.061	–0.49	0.62
Location (bilobar *vs*. less)	–0.12	0.062	–1.9	0.06
Location (liver isolated *vs*. other)	0.086	0.065	1.3	0.19
Baseline toxicity	0.79	0.047	16.6	<0.0001
ECOG (0 *vs*. other)	0.84	0.14	0.61	0.54
Portal vein (patent *vs*. any thrombus)	–0.059	0.088	–0.67	0.50
BMI	0.011	0.0039	2.79	0.0056
Lung shunt	–0.0078	0.0059	–1.31	0.19
Tumor volume (%)	–0.0002	0.0018	–0.11	0.91
Delivered activity	–0.003	0.0019	–1.38	0.17
Treatment area (whole liver *vs*. other)	0.0003	0.065	0.00	0.99

ECOG, Eastern Cooperative Oncology Group; BMI, body-mass index.

Table 8 Linear regression of predicting demographics for grade 3 bilirubin toxicity

Variable	Coefficient	Standard error	*t*	Prob (> l t l)
Intercept	2.10	2.1	1.0	0.31
Age	–0.024	0.019	–1.2	0.23
Gender (male)	0.42	0.43	0.96	0.34
Race (Black *vs*. other)	–0.36	0.69	–0.52	0.61
Race (White *vs*. other)	0.57	0.64	0.89	0.38
Cancer type (metastatic *vs*. other)	0.34	0.51	0.67	0.50
Location (bilobar *vs*. less)	–0.042	0.44	–0.09	0.92
Location (liver isolated *vs*. other)	–0.29	0.46	–0.63	0.53
Baseline toxicity	2.8	0.76	3.7	0.0002
ECOG (0 *vs*. other)	–0.21	0.53	–0.4	0.69
Portal vein (patent *vs*. any thrombus)	–0.89	0.92	–0.97	0.33
BMI	–0.045	0.028	–1.7	0.099
Lung shunt	0.056	0.05	1.1	0.26
Tumor volume (%)	–0.004	0.012	–0.36	0.72
Delivered activity	0.0085	0.011	0.76	0.45
Treatment area (whole liver *vs*. other)	0.96	0.48	2.0	0.046

ECOG, Eastern Cooperative Oncology Group; BMI, body-mass index.

Table 9 Summary of statistically significant findings for Linear Regression of ALT, AST and INR

Value	Co-efficient	Standard error	*t*	Probability (> I t I)
ALT				
Age	–0.96	0.40	–2.4	0.017
Race (White *vs*. other)	26.8	10.4	2.58	0.01
Baseline toxicity	0.74	0.22	3.41	0.0007
Tumor volume	–0.74	0.35	–2.12	0.035
AST				
White	43.93	16.34	2.69	0.007
Baseline toxicity	1.37	0.36	3.78	0.0002
INR				
Tumor volume	–0.022	0.01	–2.14	0.03
ECOG (>1 *vs*. 0)	0.47	0.22	2.17	0.03
Portal vein patent	–0.9	0.39	–2.32	0.02

ALT, alanine aminotransferase; AST, aspartate transaminase; INR, international normalized ratio; ECOG, Eastern Cooperative Oncology Group.

In the HCC specific logistic regression, the presence of extra-hepatic disease predicted toxicity. Senthilnathan *et al*. reported a 28% incidence in the development of extrahepatic disease following locoregional therapy (27). Extrahepatic disease was most common patients with aggressive tumors. The subgroup of patients treated in the current study likely had similar tumor biology which could have contributed to post-treatment toxicity.

Salem *et al*. have described selection bias in HCC treatment with operators preferentially choosing radioembolization over chemoembolization to treat patients with advanced HCC (28). Twenty-seven percent of their group received systemic therapy, which is indicated for advanced HCC (29). In the current group, 14.3% of HCC patients also received second and third-line systemic regimens and 38.6% also underwent locoregional therapy.

Treatment naive patients have lower toxicity rates in radioembolization trials. First-line TARE in patients with intermediate to advanced HCC in the SIRveNIB and SARAH trials had a 3% grade 3 hyperbilirubinemia risk, 0.8% risk of grade 3 albumin toxicity and a 4% risk of grade 3 ascites (30,31). Conversely, combination of TARE with sorafenib increases toxicity rates. Ricke *et al*. reported

Table 10 Logistic regression of factors associated with likelihood of any grade 3 toxicity for hepatocellular carcinoma

Value	Co-efficient	Standard error	*t*	Probability (> I t I)
Gender: male	0.2	0.8	0.3	0.8
Age	–0.01	0.03	–0.5	0.6
BMI	0.0	0.0	–0.6	0.5
Previous ablation	–0.9	1.2	0.8	0.5
Previous arterial embolization	–0.9	0.8	–1.1	0.3
ECOG 1 or greater	0.8	0.7	1.2	0.2
Venous invasion	0.9	0.8	1.1	0.3
Race: White *vs*. other	1.5	1.1	1.4	0.2
Lower tumor volume	0.03	0.02	1.4	0.2
Any baseline toxicity present	–1.0	0.7	–1.5	0.1
Prescribed activity	0.04	0.02	1.7	0.09
Whole-liver *vs*. other treatment area	1.1	0.6	1.7	0.09
Previous surgery	1.9	1.00	1.9	0.06
Presence of extra-hepatic disease	2.0	0.9	2.2	0.03

BMI, body-mass index; ECOG, Eastern Cooperative Oncology Group.

Table 11 Logistic regression of factors associated with likelihood of any grade 3 toxicity for colorectal carcinoma

Value	Co-efficient	Standard error	*t*	Probability (> l t l)
Gender: male	–0.09	0.9	–0.1	0.9
Age	–0.01	0.04	–0.3	0.8
Previous hepatic radiation	0.6	1.4	0.4	0.7
Previous ablation	–1.7	1.3	1.3	0.2
Previous surgery	1.9	1.4	1.4	0.2
ECOG 1 or greater	1.8	1.1	1.7	0.09
Extrahepatic disease present	1.7	0.9	1.8	0.07
≥3 lines systemic therapy	1.6	0.8	1.8	0.07
Lower tumor volume	0.07	0.03	2.1	0.03
Whole-liver *vs*. other treatment area	2.4	0.9	2.4	0.02
Any baseline toxicity present	3.0	1.1	2.8	0.006
BMI	0.03	0.01	3.0	0.003
Race: White *vs*. other	3.6	1.2	3.0	0.003
Prescribed activity	–0.09	0.03	–3.2	0.001
Previous arterial embolization	4.2	1.3	3.3	0.001

BMI, body-mass index; ECOG, Eastern Cooperative Oncology Group.

an increase of grade 3 hyperbilirubinemia from 4.4% with sorafenib alone to 14.5% (8). In a retrospective review of 26 patients, Zhan *et al.* reported 2 patients (7.7%) with grade 3 bilirubin toxicity and 4 (15.4%) with grade 3 albumin/ascites toxicity when combining radioembolization with either nivolumab or combined ipilimumab/nivolumab (15). Their group included intermediate and advanced HCC and half the patients had undergone previous intervention. Based on the results of this group, future trials in HCC should focus on treatment naive patients with normal baseline lab values, especially in light of the increasing incidence of non-alcoholic steatohepatitis and if bilobar treatment is being considered (32). As prospective trials represent an idealized patient scenario, recruitment would likely mirror that of Llovet *et al.* where 903 patients were screened to recruit 112 patients when comparing chemoembolization, embolization and best supportive care for HCC (33).

Colorectal carcinoma

The 188 colorectal carcinoma patients had the highest resection rate in this cohort (n=29, 15.5%) and the majority of patients had received 2 (n=43, 23%) or 3 or more (61, 32.6%) lines of chemotherapy. A number of patients were treated with loco-regional therapy including ablation (n=26, 13.9%), SBRT (n=12, 6.4%) and embolization (n=14, 7.5%). There were no patients with portal vein thrombosis in this group. Significant bilirubin and albumin toxicity developed in 28 (15%) and 10 (5.3%), respectively. Colorectal carcinoma was also the most common group to develop Grade 3 INR toxicity (n=5, 2.7%). In the colorectal carcinoma specific regression, baseline hepatic toxicity, previous arterial embolization, increased body-mass index, whole-liver treatment, and lower tumor volume all predicted an increased risk of Grade 3 or greater toxicity. Of note, 3 or more lines of systemic therapy did not reach the threshold as a risk for toxicity.

Toxicity following TARE increases with more chemotherapy, especially given the hepatotoxicities associated with oxaliplatin and irinotecan (16,17). The FOXFIRE global study reported a 1% grade 3 toxicity both for bilirubin and ascites when using TARE first-line combined with oxaliplatin-based chemotherapy for colorectal cancer (9). While radioembolization was well-tolerated, the failure to increase overall survival means future trials will focus on radioembolization treatment beyond first-line therapy. Beyond second-line systemic therapy, level one evidence exists for standalone

radioembolization to improve survival compared to best supportive care (34). Overall survival with systemic salvage regimens or TARE averages under one year (35,36). Over half the patients in this group required bilobar therapy so improved outcomes combining TARE and biologic, immune-, or systemic therapy should focus on patients with normal baseline liver functions (30-32).

Neuroendocrine tumor

The 56 patients with neuroendocrine tumor received a variety of pre-TARE treatments including resection (n=8, 14.3%), embolization (n=9, 16.1%), ablation (n=4, 7.1%) and SBRT (n=3, 5.4%). Additionally, 2 or 3 lines of therapy were given in 9 (16.1%) and 14 (26%) of patients. This group developed a lower rate of bilirubin and toxicity compared to HCC and colorectal cancer patients (n=2, 3.6% for both levels). The more moderate toxicity rates reflect the absence of baseline liver damage from cirrhosis or chemotherapy-associated toxicity.

Neuroendocrine tumors are undergoing an evolution in care. Approval of peptide receptor radionuclide therapy (PRRT) has led to rapid clinical integration (37). Also, since 2017, separate investigations reported a low, but demonstrable rate of chronic hepatotoxicity in neuroendocrine patients surviving several years after radioembolization (10,11). Given the availability of multiple radioactive agents to treat a group of patients with potentially prolonged survival, especially those with low-grade tumors, groups such as the North American Neuroendocrine Tumor Society are advocating caution in device selection when arterial therapy is being considered in potential future candidates for PRRT (12). Although evidence exists that patients can safely receive both therapies, this topic will require further study (14). Given the association of whole liver TARE with a low, but notable incidence of chronic toxicity, future research should focus on identifying tumor volumes/dosimetry to minimize liver toxicity (10,11).

As RESIN is an observational study, there is an inherent limitation related to potential selection bias and lack of a control arm. Objective measures of hepatic dysfunction were used to avoid variability in assessment of encephalopathy and ascites. Additionally, the mix of tumor types limits some conclusions that be made regarding dosimetry guidelines moving forward. We did not calculate tumor or pulmonary dosimetry. However, the provided activity measurements are within the Society of Interventional Radiology reporting guidelines. Sites entered data at self-monitored time points, resulting in less than 100% entry. As the data in the registry continues to mature, more focused reviews of specific tumor types will be performed. This group suffers from lead-time bias related to multiple previous treatments and the toxicity rates are almost certainly higher than in more treatment naïve patients. However, the multicenter design also reinforces that this referral pattern is common across the United States.

Conclusions

In summary, the current study demonstrates that radioembolization was well-tolerated clinically in a heavily pretreated group of patients. For primary hepatic malignancy, future clinical trials would ideally include treatment naïve patients. In patients with metastatic disease, bilobar therapy will more commonly be required. Future studies should focus primarily on baseline liver function to optimize recruitment and minimize toxicity, particularly if bilobar treatment is planned in the setting of limited tumor volume.

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Footnote

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