Journal of Hepatocellular Carcinoma

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ORIGINAL RESEARCH

Biochemical Safety of Ablative Yttrium-90 Radioembolization for Hepatocellular Carcinoma as a Function of Percent Liver Treated

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Purpose: Transarterial radioembolization can serve as an ablative therapy for early-stage hepatocellular carcinoma (HCC). Given the volumetric variability of liver segments, this study aimed to characterize the safety of ablative radioembolization by determining percent liver treated (%LT) thresholds associated with biochemical toxicity.

Patients and Methods: Patients with HCC receiving a single ablative radioembolization treatment using glass microspheres from 2017 through 2020 were reviewed. %LT was calculated as treatment angiosome volume divided by whole liver volume. Biochemical toxicities were defined as increases in Albumin-Bilirubin (ALBI) grade or Child-Pugh (CP) class compared to baseline and albumin or bilirubin adverse events (AEs) per the Common Terminology Criteria for Adverse Events. Receiver operating characteristic curves and multivariate logistic regression analyses were performed to assess the impact of %LT on toxicities.

Results: Of 141 patients analyzed, 53% (n=75) were ALBI 1, 45% (n=64) ALBI 2, 79% (n=111) CP-A, and 21% (n=30) CP-B. A %LT ≥14.5% was associated with grade/class increases in ALBI 2 ($p \leq 0.01$) and CP-B patients ($p=0.026$). In multivariate analysis, a %LT ≥14.5% was an independent predictor of increases in the ALBI 2 and CP-B groups ($p<0.01$). No significant %LT threshold was found for ALBI 1 and CP-A patients. No grade 3/4 albumin or bilirubin AEs were reported, while grade 2 AEs were related to an initial whole liver volume <1.3 L ($p \leq 0.01$).

Conclusion: Patients with ALBI 2 and CP-B liver function are less likely to have an increase in their respective grade/class when treating <14.5% of the liver using glass microspheres. ALBI 1 and CP-A patients showed no definitive %LT threshold for biochemical toxicity within the range of this study.

Keywords: hepatocellular carcinoma, radioembolization, Y-90, adverse events

Plain Language Summary

Transarterial radioembolization with ablative doses (>190 Gy) of Yttrium 90 is an effective therapy for early-stage hepatocellular carcinoma. This study found that treatments targeting ≥14.5% of the liver can predispose patients with a baseline ALBI 2 or Child-Pugh B classification to develop worsening of their liver function by 3- and 6 months post-procedure. Patients with a total liver volume <1.3 L are more likely to exhibit moderate bilirubin or albumin adverse events.

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Introduction

Transarterial radioembolization (TARE) with Yttrium-90 (^{90}Y) has emerged as a versatile treatment for patients with hepatocellular carcinoma (HCC), with

Received: 8 May 2021
Accepted: 6 July 2021
Published: 30 July 2021

neoadjuvant, definitive, and palliative applications.[1–5] Selective delivery of high dose TARE to ≤2 hepatic segments (ie, radiation segmentectomy) has shown local tumor control and survival outcomes comparable to other modalities with curative intent.[6–8] Radiation segmentectomy with a single compartment Medical Internal Radiation Dose (MIRD) ≥190 Gy correlates with pathologic tumor necrosis with little to no exposure to the adjacent non-target normal parenchyma.[9–11]

Despite the documented efficacy and safety of segmental ablative TARE, the quantitative amount of liver that can be treated with ablative doses of ^{90}Y remains to be determined. Considering the variability of treatment volumes and underlying liver function in this patient population, establishing toxicity thresholds for percent liver treated (%LT) is warranted. This study aimed to characterize the biochemical safety of ablative TARE with a single compartment MIRD dose ≥190 Gy as a function of %LT and describe toxicity trends according to the widely utilized hepatic function scoring systems (ie, Albumin-Bilirubin (ALBI) grade and Child-Pugh (CP) class). Additional associations between treatment parameters and development of biochemical toxicities were sought. A subanalysis with an MIRD dose ≥400 Gy was also performed.

Patients and Methods

Patient Selection

This study received Institutional Review Board approval and the requirement for written informed consent was waived. A retrospective chart review was performed on patients with HCC treated at a tertiary care center with TARE from January 2017 through October 2020. All patients received TARE as advised by a multidisciplinary tumor board. Inclusion criteria were primary HCC diagnosis by radiologic criteria or histopathology, a single radioembolization treatment, total single compartment MIRD ≥190 Gy, no additional locoregional interventions during the first year post-TARE, and available data for at least one of the 3-, 6- or 12-month follow-up periods. Patient baseline variables included age, sex, BMI, etiology of liver disease, Barcelona Clinic Liver Cancer (BCLC) stage, Eastern Cooperative Oncology Group (ECOG) performance status, CP class, ALBI grade and score, and Model for End-Stage Liver Disease (MELD) score. Patients were censored by time of liver transplantation, anatomic resection, or death. Those without the aforementioned events were censored at time of last encounter.

Radioembolization

Baseline magnetic resonance imaging (MRI), or contrast tomography (CT) if MRI was contraindicated, was obtained within 30 days prior to TARE. Radioembolization procedures were performed by seven experienced interventional radiologists using ^{90}Y glass microspheres (Therasphere™, Boston Scientific, Marlborough, MA) as previously published.[12] Pre-treatment mapping angiography using selective contrast-enhanced cone-beam CT (ce-CBCT) was performed to determine target angiosomes supplying tumor. Intra-arterial injection of technetium-99m labeled macroaggregated albumin with subsequent planar and single photon emission computed tomography was obtained to visualize radiotracer deposition and calculate lung shunt fractions. Dosimetry was calculated as per the single compartment MIRD model. All angiosomes received ≥190 Gy. In instances with multivessel administrations, MIRD was calculated using the cumulative treatment activity and volume.

Percent Liver Treated Calculation

Pre-TARE whole liver volume calculation was performed using Visage version 7.1.14 (Visage Imaging, San Diego, CA) based on the baseline MRI or CT. Treatment angiosome volume, defined as the volume of the angiosome or sum of multiple angiosomes targeted for radiation, was obtained from the pre-TARE ce-CBCT. %LT was calculated as treatment angiosome volume divided by pre-TARE whole liver volume.

Follow-Up and Toxicity Analysis

All patients were assessed for adverse events (AEs) via phone calls at 24 hours and two weeks after the intervention. Clinical visitation, imaging and laboratory testing were performed at one month followed by every three months during the first year post-TARE. ECOG, albumin, bilirubin, creatinine, sodium, International Normalized Ratio, platelet count, absolute lymphocyte count, and the presence of ascites (defined as any accumulation detected via follow-up imaging or physical examination) and/or encephalopathy at baseline and 3-, 6-, and 12-months post-intervention were obtained from the medical records. The corresponding parameters were used to calculate the CP class, ALBI grade and score, and MELD scores at each

time point. Procedure-related AEs were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.[13]

Statistical Analysis

Patient characteristics, laboratory and treatment parameters were reported as median (interquartile range (IQR) 25, 75) for continuous variables, and frequency (percentage) for categorical variables. Laboratory data pre- and post-TARE were compared using Friedman test. Additional analysis was performed using Wilcoxon signed-rank test for pre-intervention and each of the post-intervention measures. Categorical variables were compared using the Chi-squared or Fisher's exact test, as appropriate.

The biochemical toxicity events based on the hepatic function scoring systems were defined as increases in ALBI grade compared to baseline (ie, grade 1 to 2/3, or 2 to 3), and increases from CP-A to B/C or CP-B to C, respectively. Analysis using the MELD score could not be performed due to missing data. To determine treatment parameter thresholds for which events were observed per baseline grade/class during the follow-up periods, receiver operating characteristic (ROC) curves were used. The independent parameters included treatment angiosome volume, whole liver volume, %LT, total MIRD dose, treatment activity, total sphere number, specific activity, and number of spheres per cc. Threshold values were determined where the sum of sensitivity and specificity was highest (maximum Youden index). This was performed only for the 3- and 6-month follow-ups, as this period has been previously shown to capture procedure-related decompensations, while 12-month follow-up may be influenced by natural progression of liver disease.[14] Following the previously described methodology, ROC curve analysis to determine the relation of treatment parameters with the development of the highest reported grade of albumin or bilirubin toxicities per CTCAE criteria was performed.

The treatment parameter with the highest accuracy to predict toxicity events until 6 months (ie, %LT) was incorporated in the multivariate logistic regression analyses. To determine the average effect of any significant %LT thresholds on the change in ALBI grade or CP class in all follow-ups, the generalized estimating equations method was used.[15,16] This method was chosen as its methodology allows for the inclusion of all patients with available data for the outcome studied, without excluding those who missed or had not reached at least one of the follow-up periods. The dependent variable was defined as increased ALBI grade or CP class. The independent variables were %LT, specific activity, time, and baseline grade/class for their corresponding models. The models included specific activity (calculated as treatment activity divided by number of spheres) as this treatment parameter did not exhibit a correlation with %LT, while other relevant parameters (ie, treatment activity) exhibited a positive correlation and could lead to confounding. The parameter of time represented the multiple follow-up periods.

As a secondary endpoint, overall survival (OS) was analyzed using Kaplan-Meier curves with Log rank test for the entire cohort by ALBI grade, as well as each grade subgroup for comparison based on the established %LT threshold. All statistical analyses were conducted using SPSS version 25.0 for Windows (Armonk, NY: IBM Corp.) with statistical significance defined as a p-value <0.05.

Results

Patient and Treatment Characteristics

Fifty-two percent (n=141) out of 271 patients with HCC treated with ablative TARE during the study period met inclusion criteria. Baseline characteristics of the 141 patients included for analysis are summarized in Table 1. Median age was 68 years (range: 38–92) and 78% (n=111) were male. The most common sole predisposing risk factor for HCC was HCV (35%; n=49). Sixty-two percent (n=87) of patients were classified as BCLC stage 0-A, 17% (n=24) BCLC B, and 21% (n=30) BCLC C. ALBI grade distribution was 53% (n=75) ALBI 1 and 45% (n=64) ALBI 2. CP class distribution was 79% (n=111) CP-A and 21% (n=30) CP-B. Median ALBI and MELD scores were –2.61 (IQR –2.95, –2.13) and 9 (IQR 7, 11), respectively. Medically controlled ascites was present at the time of the intervention in 8% (n=12) of patients, and encephalopathy in 16% (n=23). A total of 6% (n=8) of patients had a pre-existing transjugular intrahepatic portosystemic shunt. During the study period, 17% (n=24) of patients received subsequent systemic therapy; 21% (n=5) with tyrosine kinase inhibitors, 50% (n=12) with immunotherapy, and 29% (n=7) received both. At last follow-up, 30% (n=43) of patients had undergone liver transplantation, and 2% (n=3) received resection.

All targeted angiosomes were administered a total MIRD dose ≥190 Gy, with a median dose of 403 Gy (IQR 303, 522; range: 190–1100) as shown in Table 2. The median treatment angiosome volume was 215 cm^3 (IQR 115, 381; range: 30–1410), median whole liver

Table 1 Patient Baseline Characteristics

Parameter (n = 141)		Median (IQR 25, 75) or n (%)
Age		68 (64, 73)
Sex	**Female** **Male**	31 (22) 111 (78)
BMI		29.8 (26.1, 34.4)
Etiology	**HCV** **NASH/ NAFLD** **Multiple** **Alcohol** **Other**	49 (35) 39 (28) 22 (16) 14 (10) 17 (12)
BCLC	**0-A** **B** **C**	87 (62) 24 (17) 30 (21)
ECOG	**0** **1** **2**	118 (84) 20 (14) 3 (2)
ALBI grade	**1** **2** **3**	75 (53) 64 (45) 2 (1)
Child-Pugh class	**A** **B** **C**	111 (79) 30 (21) 0
ALBI score		−2.61 (−2.95, −2.13)
MELD score		9 (7, 11)
Albumin (g/dl)		3.9 (3.5, 4.3)
Bilirubin (mg/dl)		0.8 (0.6, 1.2)
Lymphocyte count (x 10^9/L)		1.11 (0.69, 1.69)
Platelet count (x 10^9/L)		105 (74, 158)
INR		1.2 (1.1, 1.2)
Ascites		12 (8)
Encephalopathy		23 (16)

Abbreviations: IQR, interquartile range; BMI, body mass index; NASH/NAFLD, non-alcoholic steatohepatitis/non-alcoholic fatty liver disease; BCLC, Barcelona Clinic Liver Cancer; ECOG, Eastern Cooperative Oncology Group; ALBI, albumin-bilirubin; MELD, Model for End-Stage Liver Disease; INR, International Normalized Ratio.

volume 1698 cm^3 (IQR 1362, 2094; range: 707–3610), and median %LT 2.6% (IQR 7.3, 21.7; range: 1.3–69), with a median number of spheres per cc of angiosome of 17,000 (IQR 13,000, 26,000; range: 3000–67,000). The median treatment activity was 1.67 GBq (IQR 0.94, 2.84; range: 0.23–8) and median specific activity 527 Bq (IQR 319, 700; range: 145–2009).

Table 2 Treatment Characteristics

Variable (n = 141)	Median (IQR 25, 75)	Range
Treatment angiosome volume (mL)	215 (115, 381)	(30–1410)
Whole liver volume (mL)	1698 (1362, 2094)	(707–3610)
Percent liver treated (%)	12.6 (7.3, 21.7)	(1.3–69.0)
Total MIRD dose (Gy)	403 (303, 522)	(190–1110)
Treatment activity (GBq)	1.67 (0.94, 2.84)	(0.23–8.00)
Lung dose (Gy)	1.31 (0.66, 3.17)	(0.10–30.90)
Lung shunt fraction (%)	1.6 (1.0, 2.8)	(0.1–23.3)
Total sphere number (million)	4.0 (2.4, 6.0)	(1.2–16.6)
Specific activity (Bq)	527 (319, 700)	(145–2009)
Spheres per cc (thousands)	17 (13, 26)	(3–67)

Abbreviations: IQR, interquartile range; MIRD, Medical Internal Radiation Dose.

Procedure-Related Adverse Events

There were no major procedure-related complications. None of the patients exhibited radiation pneumonitis. Trends on laboratory and clinical parameters across follow-up periods are detailed in Table 3. Statistically significant differences in ALBI, MELD, albumin, lymphocyte count, and INR were observed at each follow-up compared to baseline, with a similar trend for total bilirubin at 3 and 12 months. Compared to baseline, 22.7% (n=32/141) of patients developed ascites by 3 months, however, this finding was most commonly perilesional and without associated sequelae and decreased to 17% (n=24) and 9% (n=14) by 6 and 12 months, respectively. Eighteen percent (n=26/141) of patients had newly documented symptoms of encephalopathy by 3-month follow-up, which reduced to 11% (n=16) and 6% (n=9) by 6 and 12 months, respectively.

ALBI grade increases compared to baseline were documented in 21% (n=28/134) of patients (baseline ALBI 1: 28%, n=20/71; ALBI 2: 13%, n=8/63) at the 3-month follow-up, 22% (n=23/104) by 6 months (ALBI 1: 29%, n=17/59; ALBI 2: 13%, n=6/45), and 25% (n=14/56) at 12 months (ALBI 1: 28%, n=10/35; ALBI 2: 19%, n=4/21). CP class increases were observed in 22% (n=24/109) at 3 months (CP-A: 23%, n=18/79; CP-B: 20%, n=6/30), 18% (n=16/91) at 6 months (CP-A: 16%, n=12/73; CP-B: 22%, n=4/18), and 31% (n=13/42) at 12 months (CP-A: 26%, n=9/34; CP-B: 50%, n=4/8).

Per CTCAE v5.0 criteria, no grade 3/4 albumin or bilirubin toxicities were reported at 3- and 6-month follow-up (Table 4). The highest documented albumin or bilirubin AEs within 6 months post ablative TARE

Table 3 Laboratory and Clinical Parameters at Baseline and Available Data at 3-, 6-, and 12-Month Follow-Up

Parameter	Median (IQR 25, 75) or n (%)				
	Baseline	3 Months	6 Months	12 Months	*p*
ALBI score	−2.61 (−2.95, −2.13)	−2.38 (−2.88, −2.04)*	−2.54 (−2.94, −2.10)*	−2.64 (−3.02, −2.01)*	0.007
MELD score	9 (7, 11)	10 (7, 14)*	10 (7, 12)*	11 (8, 15)*	<0.001
Albumin (g/dl)	3.9 (3.5, 4.3)	3.8 (3.3, 4.2)*	3.8 (3.4, 4.2)*	4.0 (3.4, 4.3)*	<0.001
Bilirubin (mg/dl)	0.8 (0.6, 1.2)	0.9 (0.6, 1.5)*	0.7 (0.5, 1.4)	0.8 (0.5, 1.5)*	0.062
Lymphocyte count (x 10^9/L)	1.11 (0.69, 1.69)	0.60 (0.42, 0.90)*	0.76 (0.53, 1.10)*	0.88 (0.52, 1.10)*	0.001
Platelet count (x 10^9/L)	105 (74, 158)	93 (61, 161)	102 (67, 166)	96 (74, 145)	0.147
INR	1.2 (1.1, 1.2)	1.2 (1.1, 1.4)*	1.2 (1.1, 1.3)*	1.2 (1.1, 1.3)*	0.009
Ascites	12 (8)	41 (29)	31 (22)	18 (13)	
Encephalopathy	23 (16)	45 (33)	30 (21)	14 (10)	

Notes: *Statistically significant difference compared to baseline. Continuous variables pre- and post-intervention were compared with Friedman test, with post hoc analysis using Wilcoxon signed-rank test for pre-intervention and each post-intervention measure.
Abbreviations: IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; ALBI, albumin-bilirubin; MELD, Model for End-Stage Liver Disease; INR, International Normalized Ratio.

Table 4 Frequency of Biochemical Adverse Events per Follow-Up Period According to the Common Terminology Criteria for Adverse Events V5.0

Parameter	Grade	n (%)		
		3 Months	6 Months	12 Months
Albumin	**Grade 1**	28 (20)	19 (13)	13 (9)
	Grade 2	14 (10)	9 (6)	4 (3)
	Grade 3	0	0	0
	Grade 4	0	0	0
Bilirubin	**Grade 1**	28 (20)	19 (13)	9 (7)
	Grade 2	9 (6)	6 (4)	5 (3)
	Grade 3	0	0	2 (1)
	Grade 4	0	0	0
Absolute lymphocyte count	**Grade 1**	11 (8)	13 (9)	4 (3)
	Grade 2	33 (23)	27 (19)	9 (6)
	Grade 3	34 (24)	15 (11)	6 (4)
	Grade 4	2 (1)	2 (1)	1 (1)
Platelet count	**Grade 1**	41 (29)	35 (25)	23 (16)
	Grade 2	26 (18)	21 (15)	9 (6)
	Grade 3	14 (10)	9 (6)	4 (3)
	Grade 4	1 (1)	0	1 (1)

were grade 2, with a frequency of 16% (n=23) at 3- and 10% (n=15) at 6 months. Grade 3/4 lymphocyte and platelet toxicities were observed at 3 months in 25% (n=36) and 11% (n=15) of patients, respectively, and at 6 months in 12% (n=17) and 6% (n=9). ROC curves to determine the relation of treatment variables with the development of grade 2 albumin or bilirubin toxicities for all patients revealed an association with a whole liver volume ≤1347 cm^3 at 3-month (AUC: 0.29 (95% CI: 0.14–0.44); sensitivity: 64% and specificity: 80%; p=0.010) and ≤1302 cm^3 at 6-month follow-up (AUC: 0.23 (95% CI: 0.07–0.40); sensitivity: 67% and specificity: 81%; p=0.008) (Supplementary Table 1). A %LT threshold of ≥14.5% was related to the development of these events as a trend at 3 months (p=0.201) and achieved statistical significance at 6 months (AUC: 0.75 (95% CI: 0.62–0.89); sensitivity: 89% and specificity: 65%; p=0.012).

Biochemical Trends as a Function of Percent Liver Treated

ROC curve analyses on the relation of treatment variables to increases in ALBI grade and CP class per baseline classification revealed %LT as the only parameter significantly related to toxicity events in both scoring systems. The %LT threshold was ≥14.5% for the baseline ALBI 2 group at 3 months (AUC: 0.84 (95% CI: 0.69–0.99); sensitivity: 87% and specificity: 73%; p=0.002) and 6 months (AUC: 0.83 (95% CI: 0.67–0.99); sensitivity: 83% and specificity: 79%; p=0.010) (Supplementary Table 2), as well as the CP-B group as a trend at 3 months (p=0.87) and reached statistical significance at 6 months (AUC: 0.87 (95% CI: 0.71–1.00); sensitivity: 100% and specificity: 85%; p=0.026) (Supplementary Table 3). For patients with a baseline ALBI 2, events at 3 months were additionally associated with a treatment angiosome volume ≥246 cm^3 (p=0.005), treatment activity ≥2.61 GBq (p=0.001), and total sphere number ≥3.6 million (p=0.019). For the baseline CP-A group, a whole liver volume ≤1714 cm^3 correlated with class increases at 6 months (p=0.024). No significant associations were found

Table 5 Multivariate Logistic Regression Analysis Using Generalized Estimating Equations (GEE) Method to Explore the Odds of Increase in ALBI Grade and Child-Pugh Class

Baseline	Predictors	Odds Ratio	95% CI	*p*
Increase in ALBI grade				
ALBI 2	%LT ≥14.5%	8.11	2.14–30.75	0.002
	%LT <14.5%	Ref		
	Time	1.54	0.83–2.87	0.172
	Specific activity	1.00	1.00–1.00	0.442
Increase in CP class				
CP-B	%LT ≥14.5%	23.02	2.63–201.16	0.005
	%LT <14.5%	Ref		
	Time	4.00	1.35–11.89	0.013
	Specific activity	1.00	1.00–1.00	0.568

Abbreviations: CI, confidence interval; ALBI, albumin-bilirubin; %LT, percent liver treated; CP, Child-Pugh; Ref, reference group.

between treatment parameters and events in the baseline ALBI 1 group.

Multivariate logistic regression analyses on the significant %LT thresholds obtained from the ROC curves revealed significant odds ratios for grade/class increases in patients in the baseline ALBI 2 (p=0.002) or CP-B (p=0.005) groups and a %LT ≥14.5% compared to patients within these classifications with smaller targeted volumes (Table 5). Patients with a baseline CP-B liver function had increased odds of decompensation to CP-C during the follow-up time independent of the treatment, representing natural progression of disease (p=0.013).

Survival Outcomes

Mean follow-up was 13.2 months (95% CI: 11.7–14.8) censored for liver transplantation or anatomic resection. Median OS per ALBI grade was not reached for the ALBI 1 group, while median OS for ALBI 2 patients was 21.5 months (95% CI: 12.6–39.7) (p<0.001). Subanalysis stratifying patients by %LT above and below the established threshold of 14.5% did not demonstrate differences in OS in either the ALBI 1 (p=0.62) or ALBI 2 groups (p=0.17).

Demises were documented in 19% (n=27) during the study period, none of which were related to TARE. Causes of death for the patients included: progressive or metastatic HCC (37%; n=10), decompensated end-stage liver disease (26%; n=7), additional primary cancer (22%; n=6), and unspecified (15%; n=4).

Subanalysis on Biochemical Toxicities with a Total MIRD ≥400 Gy

Seventy-two patients received a total MIRD ≥400 Gy, with the baseline scoring system distribution as follows: 53% (n=38) ALBI 1, 46% (n=33) ALBI 2, 74% (n=53) CP-A, and 26% (n=19) CP-B. At 3-month follow-up, grade/class increases were documented in 28% (n=10/36) baseline ALBI 1, 15% (n=5/33) ALBI 2, 27% (n=11/41) CP-A, and 21% (n=4/19) CP-B. At 6-month follow-up, events were reported in 35% (n=11/31) ALBI 1, 13% (n=3/23) ALBI 2, 15% (n=5/34) CP-A, and 9% (n=1/11) CP-B. A %LT threshold ≥25% was associated with increases at 3 months in the baseline ALBI 2 group treated with doses ≥400 Gy (AUC: 0.871 (95% CI: 0.68–1.00); sensitivity: 80% and specificity: 96%; p=0.009). No significant %LT thresholds were found for other categories.

Discussion

Due to inadequate liver remnant, portal hypertension, poor liver function, or comorbidities, not all patients are candidates for surgical treatment of HCC.[17] Tumor size, location, and multifocality can also result in ineligibility for thermal ablation.[9] TARE with selectively delivered ablative doses of ^{90}Y containing glass microspheres is an effective therapy for early-stage HCC which has been recently approved by the US Food and Drug Administration.[6,18,19] Due to gradual parenchymal devitalization over several months, TARE allows for the safe ablation of hepatic volumes equivalent to an anatomic resection without the instantaneous loss of liver function and sinusoidal reserve. While general safety has been established when treating two Couinaud segments or less, a more granular understanding of how much liver can be treated as a function of hepatic substrate has not been established. Furthermore, the volumetric variability of hepatic segments is well recognized; segment VIII may represent up to 26% of the total liver volume, while each of segments I, II, III and VI tend to represent <10%.[20] Given the high variability of hepatic segmental volume and treatment angiosomes between individuals, thresholds for %LT that can be safely treated with ablative TARE, defined as a single compartment MIRD dose >190 Gy, would aid in predicting AEs and guiding risk stratification.

While radioembolization-induced liver disease (REILD) has been reported in up to 20% of patients who received conventional, palliative dose TARE, this is most often observed in those with preexisting liver dysfunction

and in bilobar treatments.[21–23] The toxicities of large volume radioembolization that fall outside of classically defined REILD, such as aggravation of portal hypertension with otherwise preserved liver synthetic function, are less well documented. Conversely, the initial experience with radiation segmentectomy described no incidence of the classic REILD, with grade 3/4 AEs occurring in approximately 9% of patients within 3 months post-treatment.[10]

Ablative radioembolization is known to be generally well tolerated; however, it is important to establish predictability for this therapy. Under current liver transplant allocation rules, patients are now subjected to an extended biological test of time, up and above the prior 6 months, leading to a longer surveillance period.[24] As such, local therapy AEs that would preclude patients from future standard-of-care treatment should be considered with caution.

This study sought to establish safety %LT thresholds relative to hepatic substrate according to the widely utilized liver scoring systems (ie, ALBI grade and CP class) to better personalize risk stratification. Overall, increases in ALBI grade or CP class by 3 and 6 months occurred in 18–22% of patients. Ablative TARE targeting ≥14.5% of the liver was associated with more toxicity in patients with a baseline ALBI 2 or CP-B hepatic function compared to those with smaller targeted volumes. While increases in grade or class occurred in those with a baseline ALBI 1 (3 months: 28%; 6 months: 29%) and CP-A (3 months: 23%; 6 months: 16%), a %LT threshold could not be identified in these patients within the treatment range of this study. Notably, OS was not significantly different in any study group when comparing those treated for <14.5% vs ≥14.5% of the liver. For patients with a baseline ALBI 2, grade increases by 3 months were additionally associated with a treatment angiosome volume ≥246 cm^3, treatment activity ≥2.61 GBq, and total sphere number ≥3.6 million ($p<0.05$).

No grade 3/4 albumin or bilirubin toxicities occurred up to 6 months post ablative TARE. Grade 2 albumin or bilirubin AEs, which are defined as moderate by the CTCAE severity scale, had a frequency of 16% (n=23) at 3 months and 10% (n=15) at 6 months, and were associated with a %LT ≥14.5% when applied to the study cohort in toto ($p=0.012$). Notably, an initial whole liver volume <1.3 L was independently associated with the occurrence of grade 2 albumin or bilirubin AEs, regardless of %LT, suggesting that a reduced global hepatic parenchymal volume predisposes patients to a moderate decompensation post ablative TARE. Grade 3/4 absolute lymphocyte toxicities occurred in 36% (n=26) at 3 and 12% (n=17) at 6 months, however, clinically inconsequential lymphopenia is commonly reported after radioembolization.[25,26] Grade 3/4 platelet AEs were documented in 11% (n=15) and 6% (n=9) at 3 and 6 months, respectively. Despite the incidence of decreases in absolute platelet counts, no significant changes compared to baseline were found at the follow-up periods. Absence of marked thrombocytopenia following TARE indirectly suggests no indirect measure of procedure-related worsening portal hypertension.

Recent data have emerged in support of moving the ablative radioembolization dose nadir from >190 Gy to >400 Gy MIRD in light of increased pathologic necrosis.[11,27] Approximately half of the cohort in this study received a dose above 400 Gy MIRD. In this subset, a %LT threshold of 25% was significantly associated with class increase in baseline CP-B patients (vs 14.5% with a MIRD ≥190 Gy), which could be related to insufficient sample size and should be interpreted with caution. Otherwise, no distinct %LT thresholds associated with increased risk of hepatotoxicity could be found within this subgroup. Associations with other treatment variables (ie, treatment activity, total sphere number, specific activity, spheres per cc) and AEs were also sought, yet no relationship was found.

Advances in the understanding of radioembolization dosimetry have led to both safer practice and improved tumor control. Despite these developments, radioembolization dosimetry remains leveraged on large assumptions inherent to compartmental dosimetry as the ability to resolve true microsphere brachytherapy dose is not currently feasible in vivo. Further compounding these assumptions are the radiation dose microenvironment variabilities generated by differences in particle density and specific activity, tumor angiogenesis, as well as tumor biology and liver reserve. As such, future improvements in dosimetry will likely be leveraged either on superior microsphere dose simulation or on establishing stronger normative experiences within current dose methodologies, regardless of their limitations.

Limitations to this study include its retrospective nature, as not all subjects had consistently timed laboratory tests in follow-up. The established follow-up periods created a potential guarantee-time bias, despite reported causes of demise for excluded patients. Generating %LT threshold analysis by baseline hepatic function grade or

class subdivides an otherwise larger cohort and limits statistical power. Considering the expected yet variable progression of chronic liver disease, it is difficult to discern treatment toxicities from natural changes in liver function. The authors recognize the importance of clinical toxicities aside from biochemical AEs, which have been described in the literature and were not within the scope of this study. MIRD methodology incorrectly assumes uniform distribution of radiation between the tumor and liver parenchyma, yet existing safety and outcomes data, as well as the recommendation for this dose methodology in the glass microsphere instructions for use, support its use in this study. It is probable that the dose ranges analyzed in this report, if rendered into normal tissue and tumor compartments, would surpass established ablative thresholds for both (>88 and >205 Gy, respectively).[28,29] Despite interest in determining a possible association between number of spheres per cc of liver and biochemical safety, this analysis could not be adequately powered due to variable %LT. This study did not analyze other radioembolization devices or non-hepatocellular malignancies and its findings may not be applicable to these circumstances.

Conclusion

Treating primary HCC with ablative radioembolization using ^{90}Y containing glass microspheres is generally well tolerated and results in low levels of AEs. ALBI 2 and CP-B patients are less likely to sustain biochemical toxicity with a targeted %LT <14.5% with treatment doses ≥190 Gy. No definitive %LT threshold was associated with biochemical toxicity in ALBI 1 and CP-A patients within the range of this study. The development of grade 2 (ie, moderate) albumin or bilirubin AEs is more common in patients with an initial whole liver volume <1.3 L.

Abbreviations

AE, adverse event; ALBI, Albumin-Bilirubin; BCLC, Barcelona Clinic Liver Cancer; Ce-CBCT, Contrast-enhanced cone-beam computed tomography; CP, Child-Pugh; CT, computed tomography; CTCAE, Common Terminology Criteria for Adverse Events; ECOG, Eastern Cooperative Oncology Group; HCC, hepatocellular carcinoma; IQR, interquartile range; MELD, Model for End-Stage Liver Disease; MIRD, Medical Internal Radiation Dose; MRI, magnetic resonance imaging; OS, overall survival; %LT, percent liver treated; REILD, radioembolization induced liver disease; ROC, receiver operating characteristic; TARE, transarterial radioembolization; ^{90}Y, yttrium-90.

Ethical Approval and Informed Consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All liver donations were performed voluntarily with written informed consent and conducted in accordance with the Declaration of Istanbul. This retrospective, minimal risk study was approved by the Institutional Review Board (IRB) at Mayo Clinic and the requirement to obtain written informed consent was waived. Confidentiality of all collected patient data was maintained.

Consent for Publication

For this type of study consent for publication is not required.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This study did not receive financial support.

Disclosure

BB Toskich is an advisor for Boston Scientific, Sirtex Medical, Johnson and Johnson, AstraZeneca, Genentech, Eisai, HistoSonics and Turnstone Biologics. The authors reported no other potential conflicts of interest for this work.

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