JOURNAL OF INONU LIVER TRANSPLANTATION INSTITUTE

DOI: 10.14744/jilti.2026.30602
J Inonu Liver Transpl Inst 2025;3(3):108–116

Original Research

Radioembolization Effects on Liver Function and Tumor Responses in Hepatocellular Carcinoma Patients

Brian Irving Carr,[1] Volkan Ince,[1] Ertugrul Karabulut,[1] Harika Gozde Gozukara Bag,[2] Tarik Recep Kantarci,[1] Ramazan Kutlu[3]

[1]Liver Transplantation, Inonu University, Malatya, Türkiye
[2]Department of Biostatistics, Inonu University, Malatya, Türkiye
[3]Department of Radiology, Inonu University, Malatya, Türkiye

Abstract

Objectives: Transarterial radioembolization with ^{90}Y (TARE) is used as neo-adjuvant therapy for resection, liver transplant down-staging, or frontline therapy for hepatocellular carcinoma (HCC) patients. There are few reports on its use from high-throughput liver transplant or HCC institutions in the developing world.

To evaluate responses of both the liver and tumor to TARE in patients awaiting living donor liver transplant (LDLT).

Methods: HCC patients received TARE, and suitable patients then received LDLT or otherwise continued TARE till disease progression. CAT scans, liver lobe volumes and liver function tests were assessed at baseline and 3 months.

Results: Less than 10% of patients developed decreased blood albumin or platelets, or increase in total bilirubin or ALBI grade at 3 months post TARE. Many patients with abnormal baseline liver values, had an increase in albumin (42.1% patients) and platelets (64.7% patients) or decrease in total bilirubin (71.4% patients) or ALBI grade (51.5% patients) at 3 months post TARE. To explain liver function improvements, lobar liver volumes were assessed and increased in the TARE-untreated, contralateral lobe (median 17.46%) pre-Tx. AFP levels decreased in 81.8% of patients with elevated baseline AFP levels. Survival was longer in the TARE-Tx compared with unrelated TARE-non transplanted patients.

Conclusion: Liver toxicities were low, and many patients had early improvement in liver parameters post TARE.

Keywords: HCC, lobar hypertrophy, liver function, radioembolization

Please cite this article as "Carr BI, Ince V, Karabulut E, Gozukara Bag HG, Kantarci TR, Kutlu R. Radioembolization Effects on Liver Function and Tumor Responses in Hepatocellular Carcinoma Patients. J Inonu Liver Transpl Inst 2025;3(3):108–116".

Transarterial radioembolization with ^{90}Y (TARE) has increasingly become part of the therapeutic armamentarium for locoregional therapy for patients with non-metastatic hepatocellular carcinoma (HCC) in recent years, owing to its effectiveness, relatively low toxicity[1-3] and comparable survival rates to transarterial chemoembolization (TACE).[4-6] In addition it is relative safe compared with TACE in patients with portal vein thrombosis (PVT).[7,8] Despite the burgeoning literature on its use, precise knowledge is still lacking concerning its mechanisms, predictors of response and resistance, optimal uses and combinations with other treatment modalities. There is also no accurate information on the speed to or durability of HCC responses.

Address for correspondence: Brian Irving Carr, MD. Liver Transplantation, Inonu University, Malatya, Türkiye
E-mail: brianicarr@hotmail.com

Submitted Date: 11.12.2025 **Revised Date:** 08.01.2026 **Accepted Date:** 12.01.2026 **Available Online Date:** 14.01.2026
Journal of Inonu Liver Transplantation Institute - Available online at www.jilti.org

TARE has been shown to cause ipsilateral lobar or segmental atrophy, together with corresponding contralateral lobar hypertrophy, and is increasingly used as a safer substitute to portal vein embolization (PVE)[9, 10] for the preparation of patients for resection who have a potentially marginal future liver remnant (FLR) after resection.[11-14] We have explored these considerations in a series of patients who were treated with TARE for tumor control while being prepared for subsequent liver transplantation (LT). We performed targeted radioembolization therapy using either glass microspheres (Therasphere) or resin microspheres (Sirsphere), each containing radioactive ^{90}Yttrium (^{90}Y). A small proportion of these HCC patients had some expected liver toxicities[15, 16] post TARE, but we also unexpectedly found patients whose liver function improved compared with baseline values, in addition to a decrease in serum levels of alpha-fetoprotein (AFP) in patients who had elevated baseline AFP levels. We found contralateral lobar hypertrophy on routine follow-up CAT scans compared to baseline pre-TARE scans, which may explain the liver function improvement. We also consider other explanations and suggest new hypotheses for this, concerning tumor-microenvironmental interactions. If correct, this may enhance our ideas concerning the 2-way interactions between HCC and its microenvironment.

Methods

Thirty six unresectable patients with hepatocellular carcinoma (HCC) were treated with TARE to maintain tumor control while preparations were being made for living donor liver transplantation (LDLT), TARE-Tx were retrospectively analyzed.

Inclusion criteria: patients with an HCC diagnosis that was considered to be unresectable, age >18 years, absence of metastases, lung shunt <20%, prior informed consent for the radioembolization procedure and treatment; ECOG performance status <3 and adequate hematologic, renal and liver function tests for a safe interventional procedure.

Demographic and clinical characteristics of the HCC patients analyzed for this study were: age, gender, pre-TARE and last (pre-transplant) alpha-fetoprotein (AFP) and liver function values, maximal baseline tumor diameter, number of tumors (1 versus >1) and presence or absence of macroscopic portal vein invasion by tumor (PVT) on the CAT scan. The primary objective of this retrospective analysis was to examine the responses of the treated liver by liver function tests, as well as of the HCC to therapy by serum AFP level and CAT scan changes (RECIST criteria) and to identify the development of any liver toxicities. Since we unexpectedly found improved liver function in several patients, we then retrospectively looked for hypertrophy in the untreated contralateral liver lobe in the CAT scans. Radiographic liver volume and lobar assessment was performed by liver CAT scan at baseline and at 3 months post TARE, using Myrian imaging software, France.

The study protocol was approved by the ethical committee of the University institutional review board (IRB) for non-interventional studies (2025/8125) for data collection and analysis, and conducted in adherence to the Declaration of Helsinki. Since this was a non-intervention retrospective study, patient informed consent was not required for the study evaluation, although each patient signed an informed consent for the proceedure.

Diagnosis of HCC was established by percutaneous biopsy or noninvasively based on presence of a hepatic mass greater than 2 cm diameter with characteristic imaging findings in the setting of liver cirrhosis as per EASL guidelines. Treatment was performed on an inpatient basis, and patients were typically not discharged home for 24 hr after the procedure for post-TARE safety observations.

Radioembolization Procedures

Patients were treated as per published guidelines[15-17] and underwent pre-treatment angiographic mapping of the abdominal aorta and hepatic arteries. Planar scans of the lung and liver area in anterior and posterior views were acquired after injection of 99mTc-labelled albumin macroaggregated albumin (99mTc-MAA) into selected arterial branches followed by SPECT (until 2006) or SPECT/CT scans. Radioembolization was delivered using Yttrium-90 resin microspheres (SIR-Spheres; Sirtex Medical Limited, North Sydney, NSW, Australia) or glass microspheres Therasphere, Boston Scientific, Boston MA, USA). Dose calculating changed over time. Initially, the BSA method was used, but subsequently, personalized dosimetry planning, considering optimal absorbed doses by tumoral and non-tumoral volumes was used by the treating interventional radiologist.

Hepatic Volumetric Analysis

CT images (Somatom Definition, 256x256; Siemens Healthineers, GmbH, Erlangen, Germany) were used for volumetric evaluation. According to routine dynamic hepatic CT protocol, pre-contrast, thin-slice scanning and non-ionic, contrast-enhanced arterial, portal, and hepatic phase thin-slice scanning were performed. Automated volume calculation software used the data from the CT images to create estimated measurements.[17]

Clinical Evaluation

Serum laboratory analysis included complete blood count, international normalized ratio, AFP levels and comprehensive metabolic and liver panel were obtained at baseline and repeated at 1 and 3 months post TARE. Radioembolization-related toxicities were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v6.0 and the assessment of radioembolization-induced liver disease.[18] Tumor responses were evaluated by mRECIST (modified Response Evaluaton in Solid Tumors) criteria. Tumor necrosis was assessed by microscopic estimates in 5% increments.

Statistical Analysis

The normality of the quantitative data was assessed by Shapiro-Wilk test. Mann-Whitney U test was used to compare two independent groups and data were summarized by median (interquartile range). The distribution of the qualitative data was presented by count (percentage), and chi-square test was used for comparisons. Survival analyses were performed by Kaplan-Meier analysis, Log-rank test and univariate Cox regression analysis. The two-sided significance level was considered as 0.05 in all analysis. Software analysis was IBM SPSS Statistics for Windows, Version 26.0 (Armonk, NY: IBM Corp.).

Results

Liver Function Changes After TARE in Pre-transplant (TARE-Tx) HCC Patients

Liver function changes after TARE treatment are shown in Table 1, A-E. Results at 3 months post TARE showed a decrease in serum albumin levels in 8.3% percent of patients (Table 1A), all less than grade 3 toxicity by CTCAE criteria.[18] Stable levels were seen in 69.4% of patients. However, an improvement or increase in serum albumin levels was seen in 22.2% of the total patient cohort, or in 42.1% of those patients (8 of 19) who had low baseline <3.5 g/dL (abnormal) serum albumin levels (Table 1A, top row). There were similar findings for blood platelet levels, with 9.3% having decreased levels and 34.4% of the total cohort having increased platelet levels, or 64.7% of those patients (11 of 17) who had baseline thrombocytopenia <125 x103/μL, which is a reflection of portal pressure (Table 1B, top row) having increased platelet levels. Total serum bilirubin levels were increased in 9.3% of the total cohort at 3 months, all less than grade 3 toxicity, and 59.3% of patients had stable serum bilirubin levels. However, similar to the findings for albumin, 31.2% of the cohort had decreased (improved) total bilirubin levels, which was 71.4% of those patients (10 of 14) who had increased baseline serum total bilirubin levels of >1.5 mg/dL (Table 1C, bottom row). Similar results were seen for INR levels (Table 1D). ALBI levels were calculated, using MDCalc (www.mdcalc.com). A worsened (increased) grade was seen in 6% of patients at 3 months post TARE, while 51.5% (17 of 33 patients) had an improved (decreased) grade (Table 1E). Thus, there were some worsened liver function values, but a larger patient number had improvement in levels of albumin (increased), platelets (increased), total bilirubin (decreased), INR (decreased) and ALBI grade (decreased). The slight decrease in denominator patient numbers for INR and ALBI reflect some missing lab values.

Tumor Changes After TARE in Pre-transplant (TARE-Tx) HCC Patients

Baseline serum AFP levels were elevated in only 13 of 36 patients (36%) of the cohort, a figure close to what we and others have previously found.[20, 21] Two of 11 patients (18.2%) had increased AFP levels within 3 months of TARE (Table 2A), whereas 9 of 11 patients (81.8%) had decreased AFP levels, mostly by >90% at 3 months after TARE in pre-transplant patients. CAT scan-based tumor changes at 3 months (post 1 cycle of TARE) showed that 32.1% of the 36 patients had minor responses (RECIST criteria), with no partial or complete responses, but 60.7% of patients had decreased tumor vascularity (Table 2B). The transplant pathology showed an average of 58.7% necrosis in the treated HCC specimens, with 52% of patients having more than 75% of the tumor cells being necrotic (Table 2C). The variability of response by necrosis may also be a reflection of the wide time range between TARE and LDLT, being a mean of 6.3 months (range of 3 to 12 months) and a median of 5 months.

Changes in Liver Lobe Volumes in Response to TARE

TARE has previously been shown to cause atrophy in the treated liver lobe and compensatory hypertrophy in the non-treated, contralateral lobe,[11-14] which has being used to prepare for liver resection in those patients who have potential marginal future liver remnants (FLR) post resection. Since embolization- induced contralateral liver hypertrophy has been thought to be associated with improved liver function,[21, 22] we considered whether similar hypertrophy might explain the liver functional improvements found post TARE in our patients. Lobar volume changes in treated right lobes and untreated contralateral left lobe volumes are shown in Table 4. The median treated right lobe atrophy was a volume decrease of -16.4%, with a wide range from -49.01 to -5.22 percent decrease (data not shown). In contrast, hypertrophy in the untreated left lobe had a median increase of 17.46% in volume, with a similarly large range of 5.69 to 41.5% increase in the transplant (TARE-Tx) patients (Table 3).

Table 1. Blood parameter responses post TARE in pre-transplant (TARE-Tx) patients

A. Albumin. TARE-Tx	**Patients**	**Baseline – 1 mo. n (%)**	**Baseline – 3 mo. n (%)**
*Increased	Baseline low	9/21 (42.8)	8/19 (42.1)
Increased		9/36 (38.9)	8/36 (22.2)
No change	All	24/36 (66.6)	25/36 (69.4)
Decreased		3/36 (8.3)	3/36 (8.3)

*denominator reflects only those patients with abnormal baseline values.

B. Platelets. TARE-Tx	**Patients**	**Baseline – 1 mo. n (%)**	**Baseline – 3 mo. n (%)**
*Increased	Baseline low	10/17 (58.8)	11/17 (64.7)
Increased		10/36 (27.8)	11/32 (34.3)
No change	All	24/36 (66.6)	18/32 (56.2)
Decreased		2/36 (5.5)	3/32 (9.3)

*denominator reflects only those patients with abnormal baseline values

C. T. Bili. TARE-Tx	**Patients**	**Baseline – 1 mo. n (%)**	**Baseline – 3 mo. n (%)**
Increased		4/36 (11.1)	3/32 (9.3)
No change	All	19/36 (52.7)	19/32 (59.3)
Decreased		13/36 (36.1)	10/32 (31.2)
*Decreased	Baseline high	13/16 (68.7)	10/14 (71.4)

*denominator reflects only those patients with abnormal baseline values

D. INR. TARE-Tx	**Patients**	**Baseline – 1 mo. n (%)**	**Baseline – 3 mo. n (%)**
Increased		1/32 (3.1)	1/32 (3.1)
No change	All	28/32 (87.5)	27/32 (84.3)
Decreased		3/32 (9.3)	4/32 (12.5)
*Decreased	Baseline high	3/7 (42.8)	4/7 (57.1)

*denominator reflects only those patients with abnormal baseline values

E. ALBI TARE-Tx	**Patients**	**Baseline – 1 mo. n (%)**	**Baseline – 3 mo. n (%)**
Grade Increase		2/35 (5.7)	2/33 (6.0)
No change	All	18/35 (51.4)	14/33 (42.4)
Grade Decrease		15/35 (42.8)	17/33 (51.5)

ALBI - Increased: 2 to 3(1);1 to 2(1). Decreased: 2 to 1 (10); 3 to 1 (5); 3 to 2 (2). Albumin, Platelets (A, B), improvements = increased level post TARE as % of low baseline level. Bilirubin, INR (C, D), improvements = decreased level post TARE as % of elevated baseline level. ALBI (E), improvement = decreased grade post TARE compared with baseline grade.

Survival After TARE in Transplant (TARE-Tx) and Non-transplant (TARE-no Tx) Patients

Survival time for the TARE-Tx patients was significantly better than for the TARE-no Tx patients, as expected, with median survival in the transplant group not yet reached, but with a mean of 2211.29±168.97 days, compared to a mean of 1002.05±137.49 days for the non-transplant group (Table 4). The hazard ratio for death for the TARE-no Tx patients was 6.140.

Clinical Characteristics of TARE-Tx Compared with TARE-no Tx Patients

In order to try to understand the differences in the survival post TARE in the TARE-Tx versus the TARE-no Tx patients, we compared their blood biochemical and their tumor

Table 2. AFP and tumor responses post TARE in pre-transplant (TARE-Tx) patients

A.AFP.	TARE-Tx (n=13)	
	Baseline – 1 mo. n (%)	Baseline – 3 mo. n (%)
Increased	2/13 (15.4)	2/11(18.2)
No change	0	0
Decreased	11/13 (84.6)	9/11 (81.8)

B.Tumor response by CAT scan post TARE	TARE-Tx (n=28) n (%)
Minor	9 (32.1)
PR	0
CR	0
Stable	19 (67.8)
Progression	0
Vascular response	17 (60.7)

PR: Partial response; CR: Complete response.

C.Transplant tumor pathology (% necrosis)	TARE-Tx (%)
Range	5-100
Average	58.7
>75% necrosis	52

Table 3. Pre-transplant liver lobe volumes pre and post TARE (left lobe hypertrophy)

	Pre-TARE left	Post-TARE left	Change % left
Mean (mL)	552.3	657.6	20.29
Median (mL)	471	629	17.46
Min (mL)	241	312	5.69
Max (mL)	1203	1378	41.50

profiles (Table 5). The 4 tumor characteristics were all more aggressive for the TARE-no Tx versus the TARE-Tx patients. Thus, AFP levels (median 13.34 versus 64.55 IU/mL), maximum tumor diameter or MTD (median 7.5 versus 5.5 cm), percentage of patients with PVT (63.6 percent versus 33.3 percent) and tumor multifocality (66.6 percent versus 33.3 percent of patients), were all significantly worse in the non-transplant compared to the transplanted patients. These more aggressive tumor characteristic findings likely explain the reason why the TARE-no Tx patients could not be transplanted. Conversely, the liver function tests (total bilirubin, INR, GGT and platelets) were all significantly worse in the transplant group and liver transplantation is curative for liver failure. Interestingly, serum albumin levels were not significantly different, nor were the AFP levels significant, despite their similar median values, probably due to the wide range of individual values.

Discussion

TARE therapy has increasingly been used as a bridge to liver transplantation in the treatment of HCC.[24-27] Several reports have shown that contralateral hypertrophy of the non-irradiated liver occurs following TARE.[3-6] This effect has been considered useful because TARE has been shown by others to provide both tumor control as well as induction of contralateral hypertrophy, to enable improved liver function for possible planned resection surgery. TARE has superceded portal vein embolization[9, 10] for this purpose, in part for its enhanced safety compared with embolization, as well as for its concomitant tumoricidal actions. Although the current study did not involve resection, we were interested to see the rapid changes in lobar liver volumes and liver function tests post TARE, during the time these patients received TARE as a bridge to liver transplantation.

We found some grade <3, mainly transient liver toxicities, in line with the low percentage of these events reported by others[27-30] with less than 10% of patients having liver toxicities, mostly low grade and transient, as seen in changes in blood bilirubin, albumin, INR and ALBI score,[31-33] as well as platelets levels as a reflection of portal pressure (Table 1).

We also noted improvement in liver function, particularly in patients with baseline abnormal liver tests. This is shown in Table 1 as an increase with respect to baseline abnormal low values in blood levels of albumin or platelets, or a decrease in total bilirubin levels or INR, with respect to abnormal elevated baseline values. How might this improvement be explained? Others have shown an improvement in liver metabolic or other liver functions as a result of embolization- or TARE- induced lobar hypertrophy.[34-37] Therefore we used specific software (Methods) to measure pre- and post-TARE liver lobe volumes (Table 3) and found both treated

Table 4. Survival in TARE transplant (TARE-Tx) and TARE non-transplant (TARE-no Tx) patients

	Survival (days) Mean±SE	Survival (days) Median±SE	Log-Rank p	HR (95% C.I.)	HR p
TARE-no Tx (n=36)	1002.05±137.49	765.00±42.46	<0.001	6.140 (2.460-15.324)	<0.001
TARE-Tx (n=36)	2211.29±168.97	NA		reference	

Table 5. TARE pre-transplant (TARE-Tx) and TARE non-transplant (TARE-no Tx) patient characteristics

	TARE-Tx (n=36)		TARE-no Tx (n=36)		
Pre-treatment	**N**	**Median (IQR)**	**n**	**Median (IQR)**	**p**
AFP	36	13.34 (114.8)*	36	64.55 (994.05)*	0.110
ALB	35	3.3 (0.9)	36	3.2 (0.8)	0.645
T.Bili	36	1.46 (1.36)	36	0.77 (0.59)	0.001
INR	36	1.21 (0.37)	35	1.11 (0.2)	0.007
Platelets	36	118 (106.25)	36	159 (120.5)	0.025
GGT	36	105.5 (89.5)	23	144 (227)	0.033
MTD (cm)	36	5.5 (5.3)	36	7.5 (4.0)	0.008
MTD (cm) range		2-15		2.2-19.5	
PVT (Yes)	12	33.3%	21	63.6%	0.025
Multifocality (Yes)	12	33.3%	24	66.6%	0.002

*median AFP relates to those patients with elevated serum AFP levels. Tx: transplant; AFP: alpha-fetoprotein (IU/mL); ALB: albumin (g/dL); T. Bili, total bilirubin (mg/dL); GGT: gamma-glutamyl transferase (IU/mL); INR: international normalized ratio; platelets (109/L); MTD: maximum tumor diameter (cm); PVT: portal vein thrombosis (Yes).

right lobe atrophy (not shown) and contralateral untreated left lobe hypertrophy, the latter being a median of 17.46 percent expansion in untreated lobar volume. This is in line with the reported degree of hypertrophy within 3 months in the untreated lobe in 6 studies, with a range of 7-57%.[28] There has been discussion in the literature on the relationship between degree of liver hypertrophy versus liver functional increase, although any quantitative relationship is not yet clear.[35-36]

Tumor responses to TARE treatment were initially evaluated by measurement of serum alpha-fetoprotein levels, which have been shown to correlate well with TARE responses,[38, 39] and then by CT scan. Over 80% of the patients with elevated baseline AFP levels had a response by 1 month, which proved durable at 3 months in the transplant patients (Table 2). This is in line with the massive AFP responses reported by others, with 40-70% of patients showing a 90% decrease in AFP levels.[38, 40] However, only 36% of our cohort had elevated baseline AFP values and thus AFP responses could not be evaluated in the other 64% of the patients. A similar range of findings was found by others in relationship to AFP response and outcomes.[41] The CAT scans showed minor responses in 32.1% of the patients in the transplant group, but this low response rate is to be expected after a single TARE session and only 3 months post treatment.

Patients had a wide range of necrosis on transplant pathology. Despite this, with 5-100 percent of tumor cells in differing patients having necrosis, only 52 percent of patients had more than 75 percent of necrotic cells on pathology exam, similar to other reports.[27]

The fact of so much variability in liver enzymes after TARE, with some patients having (mainly minor) toxicities, whereas others showing an improvement in liver function, suggests that multiple factors could be at play. The simplest explanation is the documented contralateral lobar hypertrophy,[21, 22, 34, 35, 42] which permits a greater surgical margin of safety for planned resection in patients with otherwise uncertain post resection liver reserve/FLR. However, whether the observed 20 percent increase in untreated contralateral lobar mass is sufficient to explain an actual improvement in the liver function in some patients, has not yet been definitively addressed.

Accordingly, other explanations might be considered. It is possible that TARE kills invasive, parenchyma-destroying cancer cells. Another possibility is that HCC cells may be secreting factors that have a negative influence on liver parenchyma. The concept of the liver microenvironment secreting growth and inflammation factors that influence the tumor is now well accepted. Yet the reverse concept is also plausible, given that cancer cachexia has been recognized as a factor in advanced cancers[43-46] and cancer cells have been shown to secrete metabolic cytokines and other mediators of catabolism.[47] The speed of changes is also consistent with reports of decreases in peripheral lymphocyte levels within 24 hr of TARE.[48, 49] Hepatic immune cell changes within a few days of TARE have recently also been reported.[50] The improvement in liver function after regional liver radiation in a subset of patients reported here has also been observed by others.[34, 35, 51] Whole liver radiotherapy for liver metastases has also been reported to result in improved liver function.[52]

The heterogeneity in response does not currently have a satisfactory explanation, especially given reports of an

unclear correlation between degree of hypertrophy and relatvely greater improvements in liver function.[53, 54] This suggests the possibility of factors other than lobar volume expansion in explaining the liver function improvements post TARE.

The survival data show that TARE followed by transplantation resulted in better survival than TARE alone, as expected. TARE was used in a our transplant group because so many of this group were borderline or outside Milan criteria with respect to tumor size, levels of serum AFP or presence of branch PVT. TARE is also considered to be a relatively safe (toxicities) and effective (decreased AFP levels and presence of necrosis on pathological examination post transplant) therapy and as a bridge to liver transplantation. The variability in time from TARE to transplant was a reflection of need to downstage the tumor or the requirements for procuring a donor liver in a country in which cadaveric organs are uncommon. However, the differences in survival between the transplanted and untransplantable patients could also have been attributable to the more aggressive and larger tumors in the untransplantable group. Thus, even without transplantation, the median survival of over 2 years for TARE patients was superior to survival reported for Sorafenib in recent clinical trials.[23] However, the 2 groups were not entirely comparable (Table 5), as the non-transplant patients had more aggressive HCC characteriststics, which made them non-transplantable.

Strengths and Weaknesses

This study adds to the literature on the incredible potential of the liver for regeneration and repair and to reports that radiation can cause both hepatototoxicity and also repair of liver damage, despite unclear mechanisms. It also implies that radioembolization appears increasingly attractive as a method for maintaining or diminishing HCCs during the wait for liver transplantation, as well as the continued evaluation of TARE as a possible mode of tumor downstaging in patients who present beyond the current criteria for liver transplantation for HCC.

There are also several limitations to this report, including its retrospective nature and the small numbers of TARE-Tx patients involved in this single institution study (n=36). Our post TARE evaluations, including serum liver parameters and AFP levels, CAT scan changes and pathology were measured at quite short times post TARE and thus likely under-estimate responses to therapy. Also, most of our patients were HBV-based and it is unclear how applicable the findings are to HCCs of other etiologies. The fact that the AFP-positive patients were less than 50 percent of the total is a reminder that AFP positive and negative HCCs may have different biologies and reinforces the need for better and more generally applicable HCC biomarkers. Interestingly, the first follow up of all these patients was at 1 month post TARE, during which many of the TARE-induced changes had already occurred.

Conclusion

Radioembolization has become a relatively safe and effective treatment for patients with advanced non-metastatic HCC (the majority). It has also helped us to study the very complex dynamics of the human liver as a result of radioembolization and highlighted both radiation-induced toxicity and radiation-induced improvements in liver function.

Disclosures

Ethics Committee Approval: Inonu Transplant Institute database management conforms to Turkish legislation on privacy and this study conforms to the ethical guidelines of the World Medical Association, Declaration of Helsinki. university IRB approval was 2025/8125 for retrospective analysis of de-identified HCC patients.

Funding: This work was supported in part by NIH grant CA 82723 (BIC).

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors declare no conflict of interest. All authors have read and agree with the contents of this paper.

Data Availability: The data are available on request to the authors, as they are not publicly available, on legal grounds. However, all analyzed data were included in the article. Any further enquiries should be directed to the corresponding author.

AI: no use was made of artificial intelligence (AI)– assisted technologies (such as Large Language Models [LLMs], chatbots, or image creators) in the production of submitted work.

Authorship Contributions: Concept – B.I.C.; Design – B.I.C.; Materials – R.K.; Analysis and/or interpretation – E.K., H.B., T.K.; Writing – B.I.C.; Critical review – V.I.

References

1. Salem R, Thurston KG, Carr BI, Goin JE, Geschwind JF. Yttrium-90 microspheres: radiation therapy for unresectable liver cancer. J Vasc Interv Radiol 2002;13(9 Pt 2):S223-9.
2. Maleux G, Albrecht T, Arnold D, Bargellini I, Cianni R, Helmberger T, et al. CIRT Principal Investigators. Predictive Factors for Adverse Event Outcomes After Transarterial Radioembolization with Yttrium-90 Resin Microspheres in Europe: Results from the Prospective Observational CIRT Study. Cardiovasc Intervent Radiol 2023;46(7):852-867.
3. Carr BI, Kondragunta V, Buch SC, Branch RA. Therapeutic equivalence in survival for hepatic arterial chemoembolization and yttrium 90 microsphere treatments in unresectable hepatocellular carcinoma: a two-cohort study. Cancer 2010;116(5):1305-14.
4. Salem R, Lewandowski RJ, Kulik L, Wang E, Riaz A, Ryu RK, et

al. Radioembolization results in longer time-to-progression and reduced toxicity compared with chemoembolization in patients with hepatocellular carcinoma. Gastroenterology 2011;140(2):497-507.e2.
5. Salem R, Gabr A, Riaz A, Mora R, Ali R, Abecassis M, et al. Institutional decision to adopt Y90 as primary treatment for hepatocellular carcinoma informed by a 1,000-patient 15-year experience. Hepatology 2018;68(4):1429-1440.
6. Kulik LM, Carr BI, Mulcahy MF, Lewandowski RJ, Atassi B, Ryu RK, et al. Safety and efficacy of 90Y radiotherapy for hepatocellular carcinoma with and without portal vein thrombosis. Hepatology 2008;47(1):71-81.
7. Martelletti C, Ricotti A, Gesualdo M, Carucci P, Gaia S, Rolle E, et al. Radioembolization vs sorafenib in locally advanced hepatocellular carcinoma with portal vein tumor thrombosis: A propensity score and Bayesian analysis. J Dig Dis 2021;22(8):496-502.
8. Shindoh J, D Tzeng CW, Vauthey JN. Portal vein embolization for hepatocellular carcinoma. Liver Cancer 2012;1(3-4):159-67.
9. Shinkawa H, Takemura S, Tanaka S, Kubo S. Portal Vein Embolization: History and Current Indications. Visc Med 2017;33(6):414-417.
10. Gaba RC, Lewandowski RJ, Kulik LM, et al. Radiation lobectomy: preliminary findings of hepatic volumetric response to lobar yttrium-90 radioembolization. Ann Surg Oncol 2009;16:1587–1596.
11. Edeline J, Lenoir L, Boudjema K, et al. Volumetric changes after (90)y radioembolization for hepatocellular carcinoma in cirrhosis: an option to portal vein embolization in a preoperative setting? Ann Surg Oncol 2013;20:2518–2525.
12. Fernández-Ros N, Silva N, Bilbao JI, et al. Partial liver volume radioembolization induces hypertrophy in the spared hemiliver and no major signs of portal hypertension. HPB (Oxford) 2014;16:243–249.
13. Birgin E, Rasbach E, Seyfried S, Rathmann N, Diehl SJ, Schoenberg SO, et al. Contralateral Liver Hypertrophy and Oncological Outcome Following Radioembolization with 90Y-Microspheres: A Systematic Review. Cancers (Basel) 2020;12(2):294.
14. Lewandowski RJ, Sato KT, Atassi B, Ryu RK, Nemcek AA Jr, Kulik L, et al. Radioembolization with 90Y microspheres: angiographic and technical considerations. Cardiovasc Intervent Radiol. 2007;30(4):571-92.
15. Salem R, Thurston KG. Radioembolization with 90Yttrium microspheres: a state-of-the-art brachytherapy treatment for primary and secondary liver malignancies. Part 1: Technical and methodologic considerations. J Vasc Interv Radiol 2006;17(8):1251-78.
16. Miller FH, Lopes Vendrami C, Gabr A, Horowitz JM, Kelahan LC, Riaz A, Salem R, Lewandowski RJ. Evolution of Radioembolization in Treatment of Hepatocellular Carcinoma: A Pictorial Review. Radiographics 2021;41(6):1802-1818.
17. Baskiran A, Kahraman AS, Cicek IB, Sahin T, Isik B, Yilmaz S. Preoperative evaluation of liver volume in living donor liver transplantation. North Clin Istanb 2017;5(1):1-5.
18. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE). Version 6.0; National Institutes of Health: Bethesda, MA, USA, 2018.
19. Carr BI. Volkan I, Bag HG, Kutlu R, Yilmaz S. Transplant versus non-transplant hepatocellular carcinoma patient characteristics and survival. World J. of Medical Oncology 2025;10:109.
20. Galle PR, Foerster F, Kudo M, Chan SL, Llovet JM, Qin S, Schelman WR, Chintharlapalli S, Abada PB, Sherman M, Zhu AX. Biology and significance of alpha-fetoprotein in hepatocellular carcinoma. Liver Int 2019;39(12):2214-2229.
21. Meier RP, Toso C, Terraz S, Breguet R, Berney T, Andres A, Jannot AS, Rubbia-Brandt L, Morel P, Majno PE. Improved liver function after portal vein embolization and an elective right hepatectomy. HPB (Oxford) 2015;17(11):1009-18.
22. Rassam F, Olthof PB, van Lienden KP, Bennink RJ, Besselink MG, Busch OR, van Gulik TM. Functional and volumetric assessment of liver segments after portal vein embolization: Differences in hypertrophy response. Surgery 2019;165(4):686-695.
23. Tan DJH, Tang ASP, Lim WH, Ng CH, Nah B, Fu C, et al. Survival Trends in Sorafenib for Advanced Hepatocellular Carcinoma: A Reconstructed Individual Patient Data Meta-Analysis of Randomized Trials. Liver Cancer 2023;12(5):445-456.
24. Tohme S, Sukato D, Chen HW, Amesur N, Zajko AB, Humar A, et al. Yttrium-90 radioembolization as a bridge to liver transplantation: a single-institution experience. J Vasc Interv Radiol (2013) 24(11):1632–8.
25. Kulik LM, Atassi B, van Holsbeeck L, Souman T, Lewandowski RJ, Mulcahy MF, et al. Yttrium-90 microspheres (TheraSphere) treatment of unresectable hepatocellular carcinoma: downstaging to resection, RFA and bridge to transplantation. J Surg Oncol (2006) 94(7):572.
26. Goswami P, Adeniran OR, K Frantz S, Matsuoka L, Du L, Gandhi RT, et al. Overall survival and toxicity of Y90 radioembolization for hepatocellular carcinoma patients in Barcelona Clinic Liver Cancer stage C (BCLC-C). BMC Gastroenterol 2022;22(1):467.
27. Braat AJ, Huijbregts JE, Molenaar IQ, Borel Rinkes IH, van den Bosch MA, Lam MG. Hepatic radioembolization as a bridge to liver surgery. Front Oncol 2014;4:199.
28. Frantz S, Matsuoka L, Vaheesan K, Petroziello M, Golzarian J, Wang E, et al. Multicenter Evaluation of Survival and Toxicities of Hepatocellular Carcinoma following Radioembolization: Analysis of the RESiN Registry. J Vasc Interv Radiol 2021;32(6):845-852.
29. Chen K, Tong AKT, Moe FNN, Ng DCE, Lo RHG, Gogna A, et al. The Impact of Radiation Dose and Tumour Burden on Outcomes in Hepatocellular Carcinoma: 11-Year Experience in a 413-Patient Cohort Treated with Yttrium-90 Resin Microsphere Radioembolisation. Liver Cancer 2024;14(2):158-179.
30. Gui B, Weiner AA, Nosher J, et al. Assessment of the Albumin-Bilirubin (ALBI) Grade as a Prognostic Indicator for Hepatocellular Carcinoma Patients Treated With Radioembolization. Am J Clin Oncol 2018;41:861-6.
31. Antkowiak M, Gabr A, Das A, et al. Prognostic Role of Albumin,

Bilirubin, and ALBI Scores: Analysis of 1000 Patients with Hepatocellular Carcinoma Undergoing Radioembolization. Cancers 2019;11:879. 10.3390/cancers11060879 On sub-analyses, serum albumin (not bilirubin) appears to be the main driver of survival prediction. Our study supports the prognostic ability of ALBI and may suggest a role of albumin alone as a biomarker for patients with HCC.

32. Toyoda H, Johnson PJ. The ALBI score: From liver function in patients with HCC to a general measure of liver function. JHEP Rep. 2022;4(10):100557.
33. Ricke J, Schinner R, Seidensticker M, Gasbarrini A, van Delden OM, Amthauer H, et al. Liver function after combined selective internal radiation therapy or sorafenib monotherapy in advanced hepatocellular carcinoma. J Hepatol 2021;75(6):1387-1396.
34. Imada H, Kato H, Yasuda S, Yamada S, Yanagi T, Hara R, et al. Compensatory enlargement of the liver after treatment of hepatocellular carcinoma with carbon ion radiotherapy - relation to prognosis and liver function. Radiother Oncol 2010;96(2):236-42.
35. Garlipp B, Amthauer H, Kupitz D, Grosser OS, Jürgens J, Damm R, et al. The Impact of Unilateral 90Y-radioembolization on Functional Changes in the Contralateral Hepatic Lobe: The Prospective, Open-label RadioEmbolization, Volumetry, and Liver FuncTion Measurements (REVoluTion) Study. Ann Surg Open 2021;2(3):e095.
36. Birgin E, Rasbach E, Seyfried S, Rathmann N, Diehl SJ, Schoenberg SO, et al. Contralateral Liver Hypertrophy and Oncological Outcome Following Radioembolization with 90Y-Microspheres: A Systematic Review. Cancers (Basel) 2020;12(2):294.
37. Memon K, Kulik L, Lewandowski RJ, Wang E, Ryu RK, Riaz A, et al. Alpha-fetoprotein response correlates with EASL response and survival in solitary hepatocellular carcinoma treated with transarterial therapies: a subgroup analysis. J Hepatol 2012;56(5):1112-1120.
38. Riaz A, Ryu RK, Kulik LM, Mulcahy MF, Lewandowski RJ, Minocha J, et al. Alpha-fetoprotein response after locoregional therapy for hepatocellular carcinoma: oncologic marker of radiologic response, progression, and survival. J Clin Oncol 2009;27(34):5734-42.
39. Iñarrairaegui M, Martinez-Cuesta A, Rodríguez M, Bilbao JI, Arbizu J, Benito A, et al. Analysis of prognostic factors after yttrium-90 radioembolization of advanced hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2010;77(5):1441-8.
40. Ng CWQ, Bin Hassan MJ, Goh C, Tong AKT, Tham WY, Thang SP, et al. Safety and Efficacy of 90Y Selective Internal Radiation Therapy Using Glass Microspheres in Hepatocellular Carcinoma: A Southeast Asian Single-Institution Initial Experience. J Nucl Med Technol 2024;52(2):148-151.
41. Teyateeti A, Mahvash A, Long JP, Abdelsalam ME, Avritscher R, Chasen B, et al. Survival outcomes for Yttrium-90 transarterial radioembolization with and without Sorafenib for unresectable hepatocellular carcinoma patients. J Hepatocell Carcinoma 2020;7:117–31.
42. Vouche M, Degrez T, Bouazza F, Delatte P, Galdon MG, Hendlisz A, et al. Sequential tumor-directed and lobar radioembolization before major hepatectomy for hepatocellular carcinoma. World J Hepatol 2017;9(36):1372-1377.
43. Nishikawa H, Goto M, Fukunishi S, Asai A, Nishiguchi S, Higuchi K. Cancer Cachexia: Its Mechanism and Clinical Significance. Int J Mol Sci 2021;22(16):8491.
44. Setiawan T, Sari IN, Wijaya YT, Julianto NM, Muhammad JA, Lee H, Chae JH, Kwon HY. Cancer cachexia: molecular mechanisms and treatment strategies. J Hematol Oncol 2023;16(1):54.
45. Rich NE, Phen S, Desai N, Mittal S, Yopp AC, Yang JD, Marrero JA, Iyengar P, Infante RE, Singal AG. Cachexia is Prevalent in Patients with Hepatocellular Carcinoma and Associated with Worse Prognosis. Clin Gastroenterol Hepatol 2022;20(5):e1157-e1169.
46. Pawarode A, Voravud N, Sriuranpong V, Kullavanijaya P, Patt YZ. Natural history of untreated primary hepatocellular carcinoma: a retrospective study of 157 patients. Am J Clin Oncol 1998;21(4):386-91.
47. Fonseca GWPD, Farkas J, Dora E, von Haehling S, Lainscak M. Cancer Cachexia and Related Metabolic Dysfunction. Int J Mol Sci 2020;21(7):2321.
48. Carr BI, Metes DM. Peripheral blood lymphocyte depletion after hepatic arterial 90Yttrium microsphere therapy for hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 2012;82(3):1179-84.
49. Estrade F, Lescure C, Muzellec L, Pedrono M, Palard X, Pracht M, et al. Lymphocytes and Neutrophil-to-Lymphocyte Ratio Variations After Selective Internal Radiation Treatment for HCC: A Retrospective Cohort Study. Cardiovasc Intervent Radiol 2020;43(8):1175-1181.
50. Öcal E, Alunni-Fabbroni M, Piseddu I, Thaler M, Zacherl MJ, Salvermoser L, et al. Immune Modulation in Untreated, Contralateral Hepatic Metastases after Yttrium-90 Radioembolization of Microsatellite Stable Colorectal Cancer. J Vasc Interv Radiol 2024;35(12):1793-1805.e4.
51. Yeo SG, Kim DY, Kim TH, Kim SY, Hong YS, Jung KH. Whole-liver radiotherapy for end-stage colorectal cancer patients with massive liver metastases and advanced hepatic dysfunction. Radiat Oncol 2010;5:97.
52. Yeo SG, Kim DY, Kim TH, Kim SY, Hong YS, Jung KH. Whole-liver radiotherapy for end-stage colorectal cancer patients with massive liver metastases and advanced hepatic dysfunction. Radiat Oncol 2010;5:97.
53. Hirai I, Kimura W, Fuse A, Suto K, Urayama M. Evaluation of preoperative portal embolization for safe hepatectomy, with special reference to assessment of nonembolized lobe function with 99mTc-GSA SPECT scintigraphy. Surgery 2003;133(5):495-506.
54. de Graaf W, van Lienden KP, van den Esschert JW, Bennink RJ, van Gulik TM. Increase in future remnant liver function after preoperative portal vein embolization. Br J Surg 2011;98(6):825-34.