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A Comparative Analysis of Transarterial Downstaging for Hepatocellular Carcinoma: Chemoembolization Versus Radioembolization

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Chemoembolization and other ablative therapies are routinely utilized in downstaging from United Network for Organ Sharing (UNOS) T3 to T2, thus potentially making patients transplant candidates under the UNOS model for end-stage liver disease (MELD) upgrade for hepatocellular carcinoma (HCC). This study was undertaken to compare the downstaging efficacy of transarterial chemoembolization (TACE) versus transarterial radioembolization. Eighty-six patients were treated with either TACE (n = 43) or transarterial radioembolization with Yttrium-90 microspheres (TARE-Y90; n = 43). Median tumor size was similar (TACE: 5.7 cm, TARE-Y90: 5.6 cm). Partial response rates favored TARE-Y90 versus TACE (61% vs. 37%). Downstaging to UNOS T2 was achieved in 31% of TACE and 58% of TARE-Y90 patients. Time to progression according to UNOS criteria was similar for both groups (18.2 months for TACE vs. 33.3 months for TARE-Y90, p = 0.098). Event-free survival was significantly greater for TARE-Y90 than TACE (17.7 vs. 7.1 months, p = 0.0017). Overall survival favored TARE-Y90 compared to TACE (censored 35.7/18.7 months; p = 0.18; uncensored 41.6/19.2 months; p = 0.008). In conclusion, TARE-Y90 appears to outperform TACE for downstaging HCC from UNOS T3 to T2.

Key words: Chemoembolization, downstaging, hepatocellular carcinoma, radioembolization, Yttrium-90 microspheres

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Introduction

The incidence of hepatocellular carcinoma (HCC) has risen significantly over the past 30 years, due in part to a rise in the prevalence of hepatitis C and also to more effective and earlier detection (1). Although HCC was once considered a contraindication to liver transplantation due to an initially disappointing high rate of recurrence (2), a landmark publication in 1996 demonstrated that appropriately selected patients with early HCC who underwent liver transplantation had a recurrence rate less than 10% and a survival rate similar to patients transplanted without HCC (3). Having now been corroborated by other studies, these Milan criteria remain the benchmark employed by the United Network for Organ Sharing (UNOS) for providing a priority status upgrade for patients with HCC who are otherwise candidates for liver transplantation (4). These criteria are associated with the best long-term survival rates in patients undergoing liver transplantation for unresectable HCC. A significant number of patients with more advanced stage of disease at diagnosis are not considered ideal candidates for transplantation; therefore, several downstaging strategies have been developed since conceptually the stage at transplant may determine the posttransplant outcome.

There are several advantages to downstaging HCC prior to or as a bridge to transplantation. First, the ability to successfully downstage a patient may impart insight into an individual's tumor biology and improve the selection process, therefore, potentially translating into superior posttransplant survival. On the other hand, patients with HCC who do not respond to downstaging efforts may in fact be declaring the aggressive biologic behavior of the HCC they harbor, perhaps indicating that recurrence posttransplantation is likely. Second, and from a more practical perspective, patients with HCC are only conferred the UNOS priority status upgrade if they meet the Milan (T2) criteria. Therefore, if a patient can be downstaged from T3 (no conferred listing advantage) to T2, the immediate advantage is a significant gain in status and therefore much quicker access to a potentially life-saving organ.

As selection criteria for transplantation and liver allocation policies evolve, bridging and downstaging therapies will likely continue to play an integral role in the waitlist management of patients with HCC. In the interim, novel therapies that are ablative and embolic continue to be refined in order to improve the efficacy of downstaging. The most commonly used downstaging therapies include transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) (5–9). TACE in particular has been examined closely as a downstaging treatment in recent years (10). While some investigators have cited downstaging rates of approximately 50%, the criteria for designating a patient as downstaged have often not been explicit in these reports or have deviated from strict UNOS T2 criteria based on size (11). Nevertheless, the literature has shown that progression-free survival following TACE may be indicative of less biologically aggressive tumors and hence could be used to select patients outside criteria for orthotopic liver transplantation (OLT) (8,11–13). External beam radiation therapy has been shown to be safe and effective in peripherally located HCC, although its role in downstaging has not been studied (14).

Transarterial radioembolization with Yttrium-90 microspheres (TARE-Y90) is being used as primary therapy for unresectable HCC at several large research centers in the United States. This report describes the outcome of 86 patients with T3 HCC, 43 of whom were treated with TACE and 43 of whom were treated with TARE-Y90. At the time of treatment, neither primary resection nor RFA were feasible, given the multifocality of disease, location and/or size of HCC, the presence of cirrhosis, portal hypertension or other comorbidities. The model for end-stage liver disease (MELD) upgrade on the basis of HCC was not possible, given the T3 status. Thus, the primary goal of this study was to compare the rates of downstaging in T3 patients to T2 status by strict imaging criteria treated with TACE or Y90. Secondary analyses included response rates, time-to-progression, event-free, recurrence-free and overall survival.

Materials and Methods

Between January 1, 2000 and December 31, 2008, 276 patients with unresectable HCC (without portal vein thrombosis or extrahepatic metastases) were treated at Northwestern University with TACE (n = 150) or TARE-Y90 (n = 126). Given the interest in downstaging patients to UNOS T2 transplant criteria, a subset analysis of T3 patients was undertaken. Of the patients treated, 43 (29%) TACE and 43 (34%) TARE-Y90 were stage T3 at baseline.

Prior to treatment, patients were reviewed at a multidisciplinary HCC conference that comprised transplant surgery, hepatology, medical oncology and interventional radiology. A consensus was reached that each patient would be treated with either TACE or TARE-Y90 as bridge-to-transplantation therapy with the potential for UNOS listing in properly selected downstaged patients. This study complied with the Institutional Review Board (IRB) requirements of our institution.

Evaluation and staging

Pretreatment assessment consisted of demographics, risk factors, biopsy results, comorbidities, presence or absence of cirrhosis and portal hypertension. Diagnostic imaging was performed using magnetic resonance imaging (MRI) or triphasic computerized tomography (CT). The level of underlying liver disease was staged according to Child–Turcotte–Pugh, UNOS tumor-node-metastasis (TNM) and Barcelona Clinic Liver Cancer (BCLC) classifications. Although some of the patients in this cohort were classified as Eastern Cooperative Oncology Group (ECOG) >0 at baseline, only those that exhibited cancer-related symptoms (e.g. pain) were classified as BCLC C. Otherwise, they were classified as BCLC B. Radiologists performing the baseline staging were blinded to whether the patients received transplantation in order to minimize staging bias.

TACE treatment

TACE was performed using standard techniques. Patients were admitted and hydrated prior to treatment. After receiving antibiotics, treatment was performed using 30-mg mitomycin, 30-mg adriamycin and 100-mg cisplatinum mixed with lipiodol as the drug carrier. Then, embolization using permanent occlusive particles was performed. Patients were observed in-house and managed for postembolization syndrome. Patients were discharged on antibiotics and analgesics.

TARE Yttrium-90 microsphere treatment

TheraSphere® (MDS Nordion, Ottawa, Canada) consists of insoluble glass microspheres where Y90 is an integral constituent of the glass (15,16). The mean sphere diameter ranges from 20 to 30 μm. Y90 is a pure beta emitter with a 64.1-h physical half-life (17). Dosimetry for this therapy has been discussed in detail elsewhere (17). All patients underwent pretreatment mesenteric angiography and ^{99}Tc-macroaggregated albumin (MAA) scanning to minimize the risk of nontarget embolization.

Clinical follow-up and response

All patients were followed clinically for toxicities and adverse events by following the National Cancer Institute Common Terminology Criteria v3.0. Toxicities and posttreatment-calculated MELD scores were recorded. These toxicities were censored once patients were transplanted.

Imaging analysis

Imaging reads were performed by five radiologists (RJL, RKR, KTS, FHM and RS). All imaging analyses were calculated from the date of first TACE or TARE-Y90 treatment. After initial imaging follow-up at 1 month, subsequent scans were performed at 90-day intervals. Response rate was assessed using World Health Organization (WHO) (50% decrease in cross-sectional diameter of target lesions from baseline) and European Association for the Study of the Liver (EASL) criteria (50% necrosis/avascularity in target lesions from baseline). In contradistinction to other downstaging series, the entire treated lesions were measured when assessing downstaging rather than only the enhancing portions of viable tissue (11). This was true even if there was no enhancing tissue. Since no strict imaging guidelines for downstaging have been established, this approach was deemed most conservative. Time to downstaging from T3 to T2 was also calculated. Downstaging to RFA was defined as a decrease in the maximum tumor dimension to ≤3 cm. This size was selected given the increased chance of residual disease after RFA of tumors above 3 cm (18).

Time to progression (TTP) was assessed using WHO criteria (at least 25% increase in cross-sectional diameter of target lesion from maximum response) and UNOS criteria (progression from UNOS T3 to a higher stage). For EASL, the following modified progression criterion was utilized: if new enhancement in a previously treated lesion was identified that warranted further locoregional treatment, EASL progression was recorded (19,20).

Table 1: Patient baseline/tumor characteristics/stages

Characteristic N (%)		TACE N = 43	Y90 N = 43	p-Value
Age (years)	Median	65	68	0.17
	95% CI	(58.9–67.8)	(62.8–75)	
Ethnic group	Caucasian	29 (65)	32 (73)	0.93
	Asian	4 (10)	4 (10)	
	Hispanic	4 (10)	2 (5)	
	African American	4 (10)	5 (12)	
	Other	2 (5)	0 (0)	
Gender	Male	36 (84)	38 (88)	0.76
	Female	7 (16)	5 (12)	
Etiology	Alcohol	10 (23)	9 (20)	0.75
	HCV	16 (36)	14 (33)	
	HCV + alcohol	0 (0)	4 (10)	
	HBV	6 (14)	2 (5)	
	Autoimmune hepatitis	2 (5)	1 (2)	
	NASH	0 (0)	2 (5)	
	Cryptogenic	5 (12)	8 (18)	
	Unknown	4 (10)	3 (7)	
Pretreatment bilirubin >2 mg/dL	Yes	10 (23)	6 (14)	0.4
	No	33 (77)	37 (86)	
Portal hypertension	Present	33 (77)	32 (74)	1.0
	Absent	10 (23)	11 (26)	
Tumor distribution	Solitary	23 (53)	20 (47)	0.66
	Multifocal	20 (47)	23 (53)	
Child–Pugh	A	23 (53)	24 (56)	0.78
	B	18 (42)	19 (44)	
	C	2 (5)	0 (0)	
BCLC	A	0 (0)	0 (0)	0.41
	B	37 (85)	34 (79)	
	C	4 (10)	9 (21)	
	D	2 (5)	0 (0)	

HCV = hepatitis C virus; HBV = hepatitis B virus; NASH = nonalcoholic steatohepatitis.

Since a patient with two lesions initially staged as T3 would still be classified as T3 if a new HCC developed, 'UNOS/new lesion' category was created to account for this and was defined as progression according to UNOS stage or appearance of a new lesion. Overall progression was defined as progression by WHO, EASL, UNOS or UNOS/new lesion.

Eight patients in the TACE cohort did not have follow-up imaging (early post TACE transplant n = 2, deaths from adverse events n = 3 and lost to follow-up n = 3). These patients were excluded from the imaging analyses but not from clinical/laboratory toxicity or survival analyses. All TARE-Y90 patients had imaging follow-up. Thus, tumor response and downstaging to T2 are based on 35 TACE and 43 TARE-Y90 patients.

Statistical analyses and survivals

All survival analyses were calculated from the date of first TACE or Y90 treatment. The proportions were compared using the Fisher's exact test. Independent variables were compared using the Mann–Whitney U-test while dependent variables were compared using the Wilcoxon test. The times to response, times to progression and median survivals were calculated using the Kaplan–Meier and were compared using the log-rank test (21). Median survival was calculated using both censored and uncensored to curative therapies (transplant/resection). Event-free survival (EFS) (defined as progression by WHO, EASL, UNOS stage [including drop-out rate if downstaged], appearance of new lesion or death censored to transplantation) was also determined and compared between the cohorts. Median follow-up time was determined using the reverse Kaplan–Meier estimator.

Results

Patient population

Table 1 summarizes the patient demographics for the entire cohort. The median age of the TARE-Y90 cohort was 68 years (range: 44–88); it was 65 years for TACE (range: 36–89) (p = 0.13). Diagnostic criteria included liver biopsy or radiographic evidence consistent of HCC as defined by standard guidelines (22,23).

Treatment and clinical follow-up

Treatment characteristics for all 86 patients are described in Table 2.

TACE: Patients were treated on an inpatient basis and were discharged on an average of 3 days (range 1–11) following the procedure. The mean number of treatments per patient was 2.0 (median: 2). 26 (60%) patients had grade 1/2 bilirubin toxicities and 11 (26%) patients had grade 3/4 bilirubin toxicities. The median pretreatment MELD score was 9 (95% CI 7–10.7); it was 9 (95% CI 7–11.7) after treatment. The most common postprocedure morbidity was postembolization syndrome (nausea, fatigue and low-grade fever) observed in 60% of patients.

Table 2: Treatment characteristics

Characteristic N (%)		TACE N = 43	Y90 N = 43	p-Value
Mean number of treatments (range)		2.0 (1–5)	1.8 (1–6)	–
Median number of treatments (95% CI)		2 (1–2)	1 (1–2)	0.21
Treatment type	Lobar	19 (44)	23 (53)	0.52
	Selective	24 (56)	20 (46)	
Median activity delivered to treatment site (range) (GBq)		–	1.61 (0.54–2.97)	–
Median dose administered to treatment site (range) (Gy)		–	110.2 (53–284)	–
Mean number of days hospitalized (range)		3 (1–11)	0 (-, -)	–
Median number of days hospitalized (95% CI)		2 (1–2)	0 (-, -)	<0.001

TARE-Y90: Patients were treated on an outpatient basis and were discharged on the day of treatment after 2–6 h. The mean number of treatments per patient was 1.8 (median: 1). Twenty-six (60%) patients had grade 1/2 bilirubin toxicities while 3 (7%) patients exhibited grade 3/4 bilirubin toxicities. The median pretreatment MELD score was 8 (95% CI 7–11); it was 9.5 (range: 7–11.6) after treatment. The most common treatment side effects were fatigue and transient nonspecific flu-like symptoms lasting 7–10 days, observed in 60% of patients.

Imaging analysis

Response rate: Table 3 illustrates the tumor response using WHO and EASL criteria and presents the downstaging rate. For TACE, the median pretreatment index tumor size was 5.7 cm (95% CI 4.9–9.2 cm, range: 3.2–17.6); the median posttreatment index tumor size was 4.3 cm (95% CI 3.5–6.7, range: 1.6–16.6, $p < 0.001$). For TARE-Y90, the median pretreatment index tumor size was 5.6 cm (95% CI 4.9–6.6, range: 3.2–14) and the median posttreatment index tumor size was 3.4 cm (95% CI 2.7–4.2, range: 0.8–12, $p < 0.0001$). Thirteen (37%) of the TACE patients and 26 (61%) of the TARE-Y90 showed WHO partial response (PR; $p = 0.07$). The median percentage decrease in crossproduct was 39% (95% CI 25–57) for the TACE cohort and 60% (95% CI 45–71) for the TARE-Y90 cohort ($p = 0.016$). The median time to WHO PR was 10.9 months (95% CI: 7.3, -) and 4.2 months (95% CI: 3.3–6.9) in the TACE and TARE-Y90 cohorts ($p = 0.025$). EASL complete response (CR) and PR rates were 6 (17%) and 19 (54%) in the TACE cohort; EASL CR and PR rates were 20 (47%) and 17 (39%) in the TARE-Y90 cohort. The median time to EASL PR was 1.9 months (95% CI 1.4–3.3) and 1.3 months (95% CI 1.1–2.4) in the TACE and TARE-Y90 cohorts, respectively ($p = 0.04$). The median time to EASL CR was not reached in the TACE cohort; it was 6.1 months (95% CI 4.2, -) in the TARE-Y90 cohort ($p = 0.017$).

Downstaging: Table 4 shows substratification analyses of the patients who were downstaged to T2. Successful downstaging to T2 was observed in 11 of 35 (31%) for TACE and 25 of 43 (58%) for TARE-Y90 ($p = 0.023$). The trend favoring TARE-Y90 for downstaging was maintained for all lesion sizes. The median time to UNOS downstaging was not reached in the TACE cohort; it was 3.1 months (95% CI 1.8–8.7) in the TARE-Y90 cohort ($p = 0.027$). Of the 25 successfully downstaged TARE-Y90 patients, 15 (60%) had solitary lesions. Eleven (26%) TACE and 9 (21%) TARE-Y90 patients were transplanted. One

Table 3: Imaging findings (response)

Characteristic		TACE N = 35	Y90 N = 43	p-Value
WHO	CR	0 (0)	0 (0)	0.12
	PR	13 (37)	26 (61)	
	SD	17 (49)	16 (37)	
	PD	5 (14)	1 (2)	
Median time to WHO PR (95% CI) (months)		10.9 (7.3, -)	4.2 (3.3–6.9)	0.025
EASL	CR	6 (17)	20 (47)	0.13
	PR	19 (54)	17 (39)	
	SD	9 (26)	6 (14)	
	PD	1 (3)	0 (0)	
Median time to EASL PR (95% CI) (months)		1.9 (1.4–3.3)	1.3 (1.1–2.4)	0.04
Median time to EASL CR (95% CI) (months)		- (-, -)	6.1 (4.2, -)	0.017
UNOS downstaged T3→T2		11 (31)	25 (58)	0.023
Median time to UNOS downstaging (95% CI) (months)		- (4.3, -)	3.1 (1.8–8.7)	0.027

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.

Table 4: Downstaged patients stratified according to size/distribution

Characteristic			TACE N = 35	Y90 N = 43	p-Value
Downstaged T3→T2			11 (31)	25 (58)	0.023
Median maximum tumor dimension	(range)		5.7 (3.2–17.6)	5.6 (3.2–14)	0.35
Maximum tumor dimension	<5 cm	Total (%)	11 (32)	15 (35)	0.28
		Downstaged (%)	5 (45)	10 (67)	0.42
		Not downstaged (%)	6 (55)	5 (33)	
	5–8 cm	Total (%)	12 (34)	21 (49)	0.28
		Downstaged (%)	6 (50)	13 (62)	0.72
		Not downstaged (%)	6 (50)	8 (38)	
	>8 cm	Total (%)	12 (34)	7 (16)	0.28
		Downstaged (%)	0 (0)	2 (28)	0.12
		Not downstaged (%)	12 (100)	5 (72)	
Tumor distribution	Solitary	Total (%)	21 (60)	20 (47)	0.66
		Downstaged (%)	6 (28)	15 (75)	0.005
		Not downstaged (%)	15 (72)	5 (25)	
	Multifocal	Total (%)	14 (40)	23 (53)	0.66
		Downstaged (%)	5 (36)	10 (44)	0.74
		Not downstaged (%)	9 (64)	13 (56)	

TACE and one TARE-Y90 patient was bridged/downstaged to resection. Eight (23%) and 18 (42%) patients had target lesions downstaged to RFA (< 3 cm) in the TACE and TARE-Y90 cohorts, respectively. Table 5 shows the percentage of patients with imaging follow-up with respect to follow-up time stratified by 3-month intervals. This demonstrates that both cohorts had near-identical percentage follow-up stratified by 3-month intervals, minimizing the possibility of follow-up bias.

Time to progression: Table 6 represents the data on the imaging TTP analyses using various criteria. Nine (26%) progressed using the WHO criteria in the TACE cohort; 4 of these patients initially showed WHO PR but went on to progress. Four (9%) of the patients treated with TARE-Y90 showed WHO PD; three of them were seen to have shown WHO response initially. The median time to WHO PD (analysis at the lesional level) was found to be 19.6 months (95% CI 12.4, -) for TACE; it was 48.6 months (95% CI 30.8, -) for TARE-Y90 (p = 0.008). The 1-year progression rate according to EASL criteria was 40% for TACE; it was 8% for TARE-Y90 cohort (p = 0.01). The median time to UNOS progression was 18.2 months (95% CI 17.3–19.6) for TACE; it was 33.3 months (95% CI 15.3, -) for TARE-Y90 (p = 0.098). The median time to UNOS/new lesion progression was 17.3 months (95% CI 7–22.6) for TACE; it was 32.6 months (95% CI 13.8–33.3) for TARE-Y90 (p = 0.096). The median time to overall progression was 12.8 months (95% CI 7.9–19.6) for TACE; it was 33.3 months (95% CI 17.8–33.8) for TARE-Y90 (p = 0.005).

Follow-up/survival

Table 7 summarizes the follow-up and survivals for the two cohorts. The median follow-up was 51.9 months for TACE; it was 34.1 months for TARE-Y90 (p = 0.008). The median EFS was 7.1 months (95% CI 6–10.6) for TACE; it was 17.7 months (95% CI 10.8–33.3) for TARE-Y90 (p = 0.0017). Two out of 11 of the TACE patients have recurred following OLT with a 1-year RFS of 73%; 2 out of the 9 TARE-Y90 patients have recurred following OLT with a 1-year RFS of 89%.

For TACE patients, overall survival censored to radical therapies (transplantation/resection) at 1, 2 and 3 years were 73%, 28% and 19%, respectively (median: 18.7 months); it was 77%, 59% and 45% for TARE-Y90 (median: 35.7 months) (p = 0.18). For TACE, overall survival without censoring to radical therapies (transplantation/resection) at 1, 2 and 3 years were 75%, 42% and 19% (median: 19.2 months); it was 81%, 69% and 59% for TARE-Y90 (median: 41.6 months) (p = 0.008).

Table 5: Imaging follow-up by 3-month intervals

Treatment		<3 months	3.1–6 months	6.1–9 months	>9 months
TACE	Total (% with follow-up imaging)	35 (100)	26[1] (74)	19[1] (54)	12[1] (34)
	Number downstaged[2] (%)	8 (23)	10 (38)	7 (37)	2 (17)
Y90	Total (% with follow-up imaging)	43 (100)	30[1] (70)	23[1] (53)	16[1] (37)
	Number downstaged[2] (%)	18 (42)	15 (50)	13 (57)	5 (31)

[1]Explanted and deceased patients become excluded from this time-dependent analysis.
[2]Only patients who remained downstaged (did not have UNOS progression) in a time period were considered as downstaged.

Table 6: Imaging findings–progression analyses

Characteristic		TACE N = 35	Y90 N = 43	p-Value
WHO	PD	9 (26)	4 (9)	0.07
1-year progression rate (%)		25	11	0.008
Median time to WHO PD (95% CI) (months)		19.6 (12.4, -)	48.6 (30.8, -)	
EASL	PD	7 (20)	3 (7)	0.10
1-year progression rate (%)		40	8	0.01
Median time to EASL PD (95% CI) (months)		19.6 (11.6, -)	- (25.9, -)	
UNOS	Progressed	11 (31)	10 (23)	0.45
1-year progression rate (%)		28	19	0.098
Median time to UNOS progression (95% CI) (months)		18.2 (17.3–19.6)	33.3 (15.3, -)	
UNOS/new lesion	Progressed	12 (34)	12 (28)	0.63
1-year progression rate (%)		36	22	0.096
Median time to UNOS/new lesion progression (95% CI) (months)		17.3 (7–22.6)	32.6 (13.8–33.3)	
Overall progression	Progressed	11 (31)	7 (16)	0.45
1-year progression rate (%)		32	15	0.005
Median time to overall progression (95% CI) (months)		12.8 (7.9–19.6)	33.3 (17.8–33.8)	

PD = progressive disease.

Discussion

Although OLT is a potentially curative treatment for HCC, most patients present at an advanced stage beyond transplant criteria. Thus, the ability to effectively downstage patients confers a definite advantage with respect to access to transplantation (24). Radiation therapies, such as stereotactic body or fractionated external beam, hold promise in the management of HCC. The development of enhanced radiation delivery techniques have resulted in higher doses to tumor with relative sparing of normal liver parenchyma (25). However, there are currently no data on the role of these techniques in downstaging. More recently, the role of transarterial radiation with Yttrium-90 for downstaging has been investigated (26). In this manuscript, we present a cohort comparison of 86 T3 patients treated with either TACE or TARE-Y90.

Both TACE and TARE-Y90 resulted in a statistically significant reduction in tumor size from baseline. More important, TARE-Y90 resulted in a significantly increased percentage of patients who were successfully downstaged compared with TACE. Although there was not a significant difference in the TTP by UNOS stage (i.e. T3 downstaged and then progressed, or T3 and progression), TARE-Y90 was superior in TTP measured by other parameters (such as WHO and EASL). These parameters specifically focus on the response to the target lesion as opposed to the natural history of UNOS staging (i.e. new lesions or increase in size of untreated lesions). Our study used strict size criteria to assess downstaging; varying criteria have been employed by earlier studies, thus making the comparison of downstaging rate difficult. The downstaging rate of 58% in TARE-Y90 patients in our series replicates the 55% in a separate cohort of T3 patients reported out of our institution (26). Other reports regarding downstaging

Table 7: Follow-up/survivals

Survivals for all patients (N = 86)			
Characteristic	TACE N = 43	Y90 N = 43	p-Value
Median follow-up (95% CI) (months)	51.9 (32.2–65.2)	34.1 (15.7–39.8)	0.008
Median survival (censored) (95% CI) (months)	18.7 (13–23.6)	35.7 (17.3–41.6)	0.18
Median survival (uncensored) (95% CI) (months)	19.2 (14.7–26.5)	41.6 (29.6, -)	0.008
Event-free survival (95% CI) (months)	7.1 (6–10.6)	17.7 (10.8–33.3)	0.0017
Recurrence data for transplanted patients (N = 20)			
Characteristic	TACE N = 11	Y90 N = 9	p-Value
Recurrence	2 (18)	2 (22)	–
Downstaged	6 (55)	9 (100)	–
1-year RFS rate (%)	73	89	0.18
Median RFS (95% CI) (months)	22.7 (6.8, -)	- (17, -)	

following TARE-Y90 treatment have been minimal to date. A recent publication reports a downstaging rate of 17% in TARE-Y90 patients, but this represents downstaging rates for patients at various stages. In addition, important baseline tumor characteristics, such as size, are not reported, making direct comparisons difficult (27).

Given that TTP may be a surrogate for survival benefit (28), the fact that TTP in TARE-Y90 patients was significantly higher than in TACE patients may also warrant that these findings be validated in a larger cohort. Furthermore, given the additional potential advantages of TARE-Y90 over TACE, including lower postembolization syndrome (29), no hospitalization and higher response rates, the use of TARE-Y90 may be an attractive option when attempting to downstage to transplantation, RFA or resection.

It is also of consequence that the efficacy of bridge therapy has yet to be determined with TACE (30). However, TACE continues to be the intraarterial treatment of choice in bridging T2 patients to transplant since it represents the standard of care in treating HCC (31,32). Given that our results indicate that TARE-Y90 provides patients with a higher TTP (by WHO and EASL criteria for the treated lesion), an important future analysis will involve a prospective comparison of TTP in T2 patients that are bridged to transplantation via TARE-Y90 versus those treated with another modality. Such an analysis may yield greater insight as to which therapy, if any, can maintain patients within T2 criteria for a significantly longer period of time, especially given that transplant wait times are continuing to increase (24).

It is important to note that median time to downstaging was within 6 months for both groups. Although time to downstaging has not been routinely reported, the practical value of this metric is clear when attempting to estimate how long it may take to potentially downstage to T2 and hence upgrade a patient's priority status. While it appears that downstaging from T3 to T2 generally occurs relatively soon after initial treatment (<6 months), this does not necessarily translate into equivalent periods that patients remain downstaged, as these differed in the two groups. TARE-Y90 was more advantageous in this regard. Certainly, one factor that cannot be ignored is the possibility of random selection bias, with more favorable tumor biology in the TARE-Y90 cohort. The ability to be maintained within T2 criteria is likely the result of interplay between the effectiveness of therapy and inherent biological behavior. However, the ability to downstage a patient was superior for TARE-Y90 at all follow-up times, and both cohorts had mature imaging follow-up time (Table 5). Of interest, both the TACE and TARE-Y90 groups appeared to decline in downstaging rate starting at 9 months, suggesting a potential timeline for the natural history of HCC progression.

It is important to note that there have been contradicting reports related to survival rates in patients undergoing liver-directed therapy (LDT) prior to liver transplantation (27). One group has noted a survival benefit in patients who respond to TACE prior to transplant (12). More recent results report no difference in survival of bridged patients with LDT when compared to T2 patients transplanted without undergoing bridging therapy (27). In contrast, findings from the Scientific Registry of Transplant Recipient database suggest that patients receiving ablative therapies prior to OLT had longer graft and overall 3-year survival when compared with those who did not (33). Taken together, these reports would suggest that efficacious downstaging to T2 may prove effective with respect to improving posttransplant recurrence rates.

The inferior 3-year posttransplant survival despite similar recurrence rates in the TACE group in the uncensored analysis will require additional investigation. It is possible to speculate that patients with HCC progression in the context of LDT associated with lower efficacy (TACE) may have been offered organs of inferior quality given the loss of MELD upgrade (>T2). Alternatively, a perceived sense of urgency by the transplant surgeons due to tumor progression may have precipitated the use of a marginal organ. This could impart an effect on graft and patient survival posttransplant while not allowing adequate time for HCC recurrence. This may have been a factor in our TACE survivals, where four of the early deaths following OLT were within 18 months.

This study is subject to a number of limitations. The analysis is based on individuals treated at a single institution. This is a nonrandomized cohort comparison. Also, this is inherently an imaging analysis since: (a) we did not specifically assess whether a patient was a transplant candidate by all other pretransplant evaluation parameters; for instance, an 80-year old patient who had T3 HCC but was not a transplant candidate based on age would have been included in our analysis and (b) there was certainly a selection bias since there was a tendency to treat more debilitated (and elderly) patients with TARE-Y90 given the better tolerability of the therapy. This may also account for the lower percentage of transplants in the TARE-Y90 group despite the higher rate of downstaging. There is also variability in measuring lesions following treatment for UNOS listing; conservatively, this was mitigated by capturing the entire lesion rather than only enhancing tissue. There is also the possibility of 'imaging follow-up time' bias. That is, patients treated recently with one therapy may not show downstaging compared to the other if they have longer imaging follow-up. This was not the case in this 86-patient cohort, as Table 5 demonstrates near-identical maturity of imaging follow-up between TACE and TARE-Y90 when stratified by 3-month intervals. There were also a higher percentage of patients with large tumors (>8 cm) as the index in TACE compared with TARE-Y90 (34% vs. 16%). The downstaging rate was therefore disadvantaged for TACE. Finally, these limitations highlight the need for

prospective, longitudinal studies that compare these two embolic modalities in T3 patients.

Conclusion

This cohort was analyzed from a radiographic perspective in response to two mechanistically different intraarterial embolic therapies and their respective ability to successfully downstage a patient to UNOS T2 by strict criteria. Moreover, the study examines the ability of patients treated with either therapy to remain within this stage (taking into account not only the targeted lesion(s) but also growth of untreated lesions and/or development of new lesions). While downstaging to T2 is generally accepted as an important endpoint in the transplant arena, its value as a prognostic factor in a nontransplantable cohort, while intuitively favorable, is not as well recognized. Although not all the patients were definitive transplant candidates, this analysis shows a superior ability to downstage with radiation therapy. These findings will require validation in a larger cohort. More important, this study may help elucidate the effectiveness of downstaging HCC with respect to posttransplant outcomes.

Conflict of Interest Statement

RS is an advisor to MDS Nordion.

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