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Research papers

Comparative study of post-transplant outcomes in hepatocellular carcinoma patients treated with chemoembolization or radioembolization

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ABSTRACT

Purpose: To analyze long-term outcomes in patients bridged/downstaged to orthotopic liver transplantation (OLT) by transarterial chemoembolization (TACE) or yttrium-90 radioembolization (Y90) for hepatocellular carcinoma (HCC).

Methods: 172 HCC patients who underwent OLT after being treated with transarterial liver-directed therapies (LDTs) (Y90: 93; TACE: 79) were identified. Pre-LDT and pre-OLT clinical/imaging/laboratory characteristics including United Network for Organ Sharing (UNOS) staging and alpha-fetoprotein values (AFP) were tabulated. Post-OLT HCC recurrence was assessed by imaging follow-up per standard of care. Recurrence-free (RFS) and overall survival (OS) were calculated. Uni/multivariate and sub-stratification analyses were performed.

Results: Time-to-OLT was longer in the Y90 group (Y90: 6.5 months; TACE: 4.8 months; $p = 0.02$). With a median post-OLT follow-up of 26.1 months (IQR: 11.1–49.7), tumor recurrence was found in 6/79 (8%) TACE and 8/93 (9%) Y90 patients. Time-to-recurrence was 26.6 (CI: 7.0–49.5) and 15.9 months (CI: 7.8–46.8) for TACE and Y90, respectively ($p = 0.48$). RFS (Y90: 79 months; TACE: 77 months; $p = 0.84$) and OS (Y90: 57% alive at 100 months; TACE: 84.2 months; $p = 0.57$) were similar. 54/155 patients (Y90: 29; TACE: 25) were downstaged to UNOS T2 or less. RFS hazard ratios for patients downstaged to ≤T2 versus those that were not were 0.6 (CI: 0.33–1.1) and 1.7 (CI: 0.9–3.1) respectively ($p = 0.13$). 17/155 patients (Y90: 8; TACE: 9) that were > T2 were downstaged to UNOS T2 or less (within transplant criteria). Distribution (unilobar/bilobar), AFP, and pre-transplant UNOS stage affected RFS on univariate analyses.

Conclusion: Despite longer time-to-OLT for Y90 patients, post-OLT outcomes were similar between patients bridged or downstaged by TACE or Y90. A trend towards improved RFS for downstaged patients was identified.

1. Introduction

Orthotopic liver transplantation (OLT) is the standard of care for cirrhotic patients exhibiting unresectable hepatocellular carcinoma (HCC) within Milan criteria. This corresponds to United Network for Organ Sharing classification (UNOS) T2 disease [1–3]. For these patients, OLT is considered curative given similar overall survival (OS) compared to transplanted patients without HCC [2]. The major obstacle for successful transplantation is organ shortage. Hence, allocation schemas have been developed to prioritize organ recipients based on the severity of their illness. In case of HCC, patients who are being considered for OLT, should not progress beyond UNOS T2 stage (solitary lesion < 5 cm, 3 lesions all < 3 cm) or Milan criteria in order to maintain their HCC priority. Given this, liver-directed therapies

Abbreviations: OLT, orthotopic liver transplantation; TACE, transarterial chemoembolization; Y90, yttrium-90 radioembolization; HCC, hepatocellular carcinoma; LDT, liver directed therapy; UNOS, United Network for Organ Sharing classification; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic for Liver Cancer; CP, Child-Pugh score; ECOG, Eastern Cooperative Oncology Group; IQR, interquartile range; MAA, macroaggregated albumin; MELD, model for end stage liver disease scoring system; MRI, magnetic resonance imaging; PVT, portal vein thrombosis; mRECIST, modified Response Evaluation Criteria in Solid Tumors; RFS, recurrence-free survival; RFA, radiofrequency ablation; US, ultrasound

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(LDTs) have been applied for bridging HCC in order to minimize drop-out by preventing their progression. Another application of LDT is downstaging of UNOS T3 (solitary tumor > 5 cm, or 3 nodules with at least 1 > 3 cm) to T2 [4]. The EASL/EORTC clinical practice guidelines and international consensus conference recommend neoadjuvant LDT if the waiting list exceeds six months [5,6]. In its most recent guidelines update, the American Association for the study of Liver Diseases (AASLD), recommends bridging to transplant in patients listed for OLT within OPTN T2 (Milan) criteria to decrease progression of disease and subsequent dropout from the waiting list [7]. However, AASLD does not recommend one form of liver-directed therapy over another. Bridging LDTs include radiofrequency ablation, conventional TACE, drug eluting beads (DEB-TACE) and radioembolization (Y90) [8–11].

Over the last 10 years, our group has been active in analyzing the role of Y90 radioembolization in HCC. Following establishment of safety and standardization of technique, its role in bridging/downstaging to transplantation, portal vein thrombosis, neoadjuvant to resection (radiation lobectomy), radiation segmentectomy and comparative effectiveness has been described. Improved quality-of-life (compared with TACE) and the results of a randomized study of Y90 +/− sorafenib in the bridging setting were reported [12–20]. Most recently, the results of a randomized, phase 2 clinical trial comparing the outcomes of cTACE and Y90 radioembolization in patients with HCC, showed that Y90 resulted significantly time to progression to progression (TTP) (> 26 months) than TACE (6.8 months) ($p = 0.0012$) (hazard ratio, 0.122; 95% confidence interval [CI], 0.027–0.557; $p = .007$) [21].

In 2009, we reported outcomes post-OLT comparing Y90 and TACE [4]. Since then, we have continued to prospectively follow these patients. There are limited data on long-term outcomes of transplanted patients undergoing neoadjuvant bridging/downstaging with TACE or Y90. The purpose of our study was to study OS, recurrence free-survival (RFS), location of recurrence and factors predicting recurrence in transplanted patients following TACE or Y90 [22,23].

2. Methods

2.1. Study design

This study analyzed patients undergoing OLT for HCC following LDT with TACE or Y90 between January 2003 and April 2013 in a large, comprehensive transplant center with expertise in liver-directed interventional procedures. Data from our database included clinic visits, cross-sectional imaging, interventional and surgical procedures. The study was approved by the Institutional Review Board and was Health Insurance Portability and Accountability Act compliant.

2.2. Patient cohort and treatment group classification

Patients were included in this comprehensive analysis if they had been transplanted for HCC after treatment with TACE or Y90. Patients were classified in the TACE or Y90 group depending on the 1st LDT they received, irrespective of additional treatments received before OLT. Post LDT treatments were tabulated.

2.3. TACE and Y90

TACE and Y90 consisted of transcatheter intra-arterial injection of chemotherapeutic agents (30 mg mitomycin, 30 mg adriamycin and 100 mg cisplatin emulsified with lipiodol) or Y90ttrium-loaded glass microspheres (Therasphere, BTG, London, UK), respectively. Injections were performed in a lobar, segmental or subsegmental branch of the hepatic arterial vasculature, accordingly to previously published guidelines [24,25]. Y90 treatments were preceded by a simulation angiography with injection of ^{99m}Technetium-labeled macroaggregated albumin (MAA) to prevent extrahepatic deposition of Y90-loaded microspheres. Y90 patients were treated on an outpatient basis, while TACE patients were observed for 1–2 days as inpatients for management of post-embolization syndrome. Patients underwent follow-up imaging by contrast enhanced magnetic resonance imaging.

2.4. Baseline characteristics

Baseline data at 1st LDT included gender, etiology of liver disease, method of diagnosis, age, Child-Pugh score (CP), tumor distribution, multifocality of disease, UNOS stage, presence of portal vein thrombosis (PVT), BCLC stage and serum alpha-fetoprotein (AFP). The total number of LDTs (TACE, Y90, radiofrequency ablation) and combination or cross-over in therapies were reported. Immediate pre-transplant UNOS stage and AFP levels were recorded. AFP > 13 ng/mL was chosen as the cut-off value.

2.5. Transplant eligibility and post-transplant outcomes

OLT assignment was directed by the transplant team (Transplant surgery/Hepatology/Interventional Radiology) according to guidelines using the model for end stage liver disease scoring system (MELD) with upgrading points accorded to HCC patients within transplant criteria [26]. Following transplantation, patients underwent imaging follow-up per routine institutional guidelines, which included ultra-sonography and Doppler scanning for the transplanted liver at the time of discharge. Subsequently, we performed a q3 month imaging for the first year (if high risk) followed by 6 months thereafter for 3 years. If deemed necessary, CT chest was done at 6 months interval concurrently with other imaging. The date and site (intra/extrahepatic) of HCC recurrence, as well as the date of death were determined.

2.6. Statistical analyses

Baseline, treatment and pre-OLT characteristics were reported using descriptive methods (number for categorical variables, median and interquartile range [IQR] for continuous variables), and compared between groups using the Mann–Whitney (categorical) or Fisher's exact test (continuous variables). Downstaging ability of TACE and Y90 was reported using descriptive statistics (number/proportions) and McNemar test; AFP change was assessed by Wilcoxon test. RFS and OS were estimated from first LDT using Kaplan–Meier curves and uni/multivariate analysis of predicting factors of survival were performed using the Log rank test and the Cox proportional regression model by baseline pre-OLT characteristics.

3. Results

3.1. Treatment characteristics

172 patients were transplanted for HCC: TACE $N = 79$, Y90 $N = 93$. Baseline, treatment and pre-OLT characteristics are summarized in Table 1. Median age at first LDT was 60 years (IQR: 55–65 years), with HCV as the most frequent etiology (98/172, 57%). UNOS stage, Child–Pugh class, focality and AFP were comparable at first LDT. In the TACE group, significantly more LDT treatment sessions ($p = 0.0160$) were performed pre-OLT. There were ulterior treatments after first LDT: 1 patient in the TACE group received Y90; 1 Y90 patient received subsequent TACE. One Y90 (1%) and 8 (10%) TACE patients underwent RFA before OLT. One TACE patient was treated with sorafenib prior to the 1st TACE; 2 Y90 patients had undergone previous resection for HCC, one of them also being treated with sorafenib prior to Y90. Two patients in the Y90 group had undergone partial hepatic

Table 1
Baseline characteristics.

	Median (IQR) or *n*			*p*-value
	TACE (*n* = 79)	Y90 (*n* = 93)	Total (*n* = 172)	
Age (years)	58 (54–65)	60 (57–64)	60 (55–65)	0.2310
Gender				
Male	67 (85%)	67 (72%)	134 (78%)	0.0643
Female	12 (15%)	26 (28%)	38 (22%)	
Method of diagnosis				
Imaging	49 (62%)	65 (70%)	114 (66%)	0.3320
Biopsy	30 (38%)	28 (30%)	58 (34%)	
Etiology of liver disease				
HCV	51 (65%)	47 (51%)	98 (57%)	0.4028
HBV	5 (6%)	11 (12%)	16 (10%)	
Autoimmune hepatitis	3 (4%)	1 (1%)	4 (2%)	
Alcohol	10 (12%)	14 (15%)	24 (14%)	
PBC	2 (3%)	2 (2%)	4 (2%)	
NASH	3 (4%)	6 (6%)	9 (5%)	
Cryptogenic	4 (5%)	11 (12%)	15 (9%)	
Hemochromatosis	1 (1%)	1 (1%)	2 (1%)	
UNOS stage				
T1	5 (6%)	4 (4%)	9 (5%)	0.1441
T2	51 (65%)	65 (70%)	116 (68%)	
T3	14 (18%)	14 (15%)	28 (16%)	
T4a	9 (11%)	5 (5.5%)	14 (8%)	
T4b	0	5 (5.5%)	5 (3%)	
Focality				
Solitary	46 (59%)	60 (65%)	106 (62%)	0.4338
Multifocal	33 (41%)	33 (35%)	66 (38%)	
AFP (ng/mL)	26.1 (7.2–130.8)	18.4 (5.1–250.3)	23.3 (6.8–194.6)	0.6372
Child–Pugh score				
A	40 (51%)	47 (51%)	87 (51%)	0.9860
B	36 (45%)	42 (45%)	78 (45%)	
C	3 (4%)	4 (4%)	7 (4%)	
BCLC without ECOG[a]				
0	1 (1%)	2 (2%)	3 (2%)	0.2108
A	51 (65%)	62 (67%)	113 (66%)	
B	22 (27%)	16 (17%)	38 (22%)	
C	2 (3%)	9 (10%)	11 (6%)	
D	3 (4%)	4 (4%)	7 (4%)	
Number of LDT(s)				
1	42 (53%)	70 (75%)	112 (65%)	**0.0160**
2	29 (37%)	18 (20%)	47 (28%)	
3	4 (5%)	4 (4%)	8 (4.5%)	
4	3 (4%)	1 (1%)	4 (2%)	
5	1 (1%)	0	1 (0.5%)	
First treatment type				
Lobar	18 (23%)	35 (38%)	53 (31%)	**0.046**
Selective	61 (77%)	58 (62%)	119 (69%)	
Time to transplant (months)	4.8 (2.7–7.7)	6.5 (3.7–9.9)	6.0 (3.4–9.3)	**0.0215**

[a] Given difficulty in assessing ECOG in patients with liver dysfunction, ECOG was omitted from BCLC. Statistical significance was set at $p < 0.05$.

resection (negative margins); they were included in this analysis given the development of new HCC lesions. 155/172 patients had both pre-LDT followed by pre-OLT imaging.

3.2. Pre-transplant course

A biological response assessed by AFP decrease was observed in both groups (TACE: $p = 0.0254$; Y90: $p < 0.0001$), with this outcome being more pronounced in the Y90 group (Table 2).

Out of the 14 pre-LDT T3 patients in the TACE group, 9 (64%) were downstaged and out of the 14 pre-LDT T3 patients in the Y90 group, 8 (57%) were downstaged ($p = 1$). Out of the 42 pre-LDT T2 patients in the TACE group, 16 (38%) were downstaged and 4 (10%) progressed; out of the 64 pre-LDT T2 patients in the Y90 group, 21 (32%) were downstaged and 2 (3%) progressed ($p = 0.29$).

Table 2
Change in AFP.

	Median (IQR)	Pre-treatment	Pre-transplant	*p*-value
AFP	TACE *n* = 65	31.5 (6.8–149.5)	15 (5.8–61.4)	0.0254
	Y90 *n* = 90	22.3 (5.0–277.7)	11.7 (5.3–36.5)	< 0.0001

The time to transplant was significantly longer in the Y90 group (median [IQR]: 4.8 months [2.7–7.7] for TACE and 6.5 months

Table 3
UNOS staging pre-treatment and pre-transplant.

UNOS Stage		Post-LDT		
Pre-LRT	Pre-transplant *	TACE (n=67)	Y90 (n=88)	Total (n=155)
T1	T1	0	3 (4%)	3 (2%)
	T2	5 (7%)	0	5 (3%)
T2	T1	16 (24%)	21 (23%)	37 (24%)
	T2	22 (33%)	41 (47%)	63 (41%)
	T3	3 (5%)	1 (1%)	4 (3%)
	T4a	1 (2%)	1 (1%)	2 (1%)
T3	T1	2 (3%)	2 (2%)	4 (3%)
	T2	7 (10%)	6 (7%)	13 (8%)
	T3	5 (7%)	6 (7%)	11 (7%)
T4a	T3	1 (2%)	1 (1%)	2 (1%)
	T4a	5 (7%)	3 (4%)	8 (5%)
T4b	T3	0	1 (1%)	1 (1%)
	T4b	0	2 (2%)	2 (1%)

*Rows in blue (downstaged), white (bridged) and red (progressed).

[3.7–9.9] for Y90; $p = 0.0215$) (Table 1). Out of the 5 patients with PVT before LDT (UNOS 4b), all being treated by Y90, 1 was downstaged to T3 with complete reestablishment of portal vein patency, 2 were still classified T4b; pre-OLT imaging was not available for 2 (Table 3).

3.3. Post-transplant outcomes

3.3.1. Recurrence

Post-OLT median follow-up was 26.1 months (IQR: 11.1–49.7). During this period, 6/79 (8%) TACE and 8/93 (9%) Y90 patients recurred. Sites of recurrence were similar between the groups TACE (intrahepatic $N = 1$, intrahepatic/adrenal $N = 1$, extrahepatic $N = 4$ [lymph node: $N = 2$, lung: $N = 1$ and abdominal wall: $N = 1$]) and Y90 (intrahepatic $N = 2$, intrahepatic/lung/bone $N = 1$, portal vein invasion $N = 1$, lymph node $N = 1$, lung $N = 3$). Amongst patients with PVT ($N = 5$, Y90 group), only one developed recurrence 13 months post-transplantation; his survival from transplantation was 15.2 months. For patients with HCC recurrence, the median (range) time to recurrence post-OLT was 26.6 months (7.0–49.5) for TACE group and 15.9 months (7.8–46.8) for Y90 ($p = 0.4843$). HCC recurrence after transplantation resulted in a trend of shorter OS, ($p = 0.0951$), with median OS of 43.5 months (HCC recurrence) versus 84.2 months (no HCC recurrence).

3.3.2. RFS/OS

RFS was not different between groups (TACE: 76.8 months, Y90: 79.0 months, $p = 0.71$) (Fig. 1a). The 5-year RFS probability was 63% (95% CI: 53–74%). The 5-year RFS probability for patients treated with Y90 vs. TACE was 59% (95% CI: 43–74%) and 66% (95% CI: 54–78%) respectively.

OS from the first LDT was also not different (TACE: 87.2 months, Y90: median not reached and 57% alive at 100 months, $p = 0.42$) (Fig. 1b). The 5-year OS probability was 68% (95% CI: 60–78%). The 5-year OS probability for patients treated with Y90 vs. TACE was 67% (95% CI: 52–82%) and 68% (95% CI: 57–81%) respectively.

Post-OLT OS was also not different (TACE: 84.2 months, Y90: 57% alive at 100 months, $p = 0.5654$).

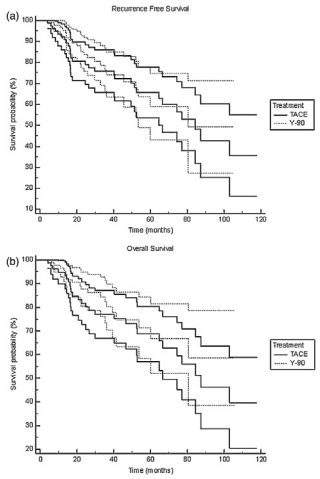

Fig. 1. (ce free survival Kaplan Meier curves (with confidence intervals) stratified by treatment; (b) overall survival Kaplan Meier curves (with confidence intervals) stratified by treatment.

3.4. Effect of pre-transplant change in stage following LDT on post-transplant outcomes

87/155 patients were bridged to transplant by Y90 (55) and TACE (32). 54/155 patients were downstaged to UNOS T2 or less by these transarterial LDTs (Y90: 29; TACE: 25). RFS hazard ratios for patients downstaged to ≤T2 versus those that were not were 0.6 (CI: 0.33–1.1) and 1.7 (CI: 0.9–3.1) respectively ($p = 0.13$). 17/155 patients that were > T2 (outside transplant criteria) were downstaged to UNOS T2 or less (within transplant criteria) by these transarterial LDTs (Y90: 8; TACE: 9).

3.5. Factors affecting RFS

By univariate analysis, RFS was found to be shorter in cases of

Table 4
Uni/multivariate analysis for recurrence free survival.

Variable	Univariate (N = 172)[a]				Multivariate (N = 149)[c]	
	Category	Hazard ratio (CI)	p-value	Adjusted p-value[b]	Hazard ratio (CI)	p-value
Gender	Female	0.96 (0.46–2.02)	0.9179	–	0.86 (0.37–2.01)	0.7343
	Male	1.00			1.00	
Age	< 60	0.97 (0.56–1.68)	0.9156	–	1.03 (0.54–1.97)	0.9173
	≥60	1.00			1.00	
Liver disease	Other	1.38 (0.78–2.41)	0.2465	–	1.45 (0.75–2.81)	0.2756
	HCV	1.00			1.00	
Distribution	Bilobar	3.01 (1.12–8.12)	**0.0006**	**0.0054**	2.28 (0.87–5.94)	0.0947
	Unilobar	1.00			1.00	
ECOG performance status	0	0.90 (0.50–1.59)	0.7048	–	0.66 (0.33–1.32)	0.2420
	> 0	1.00			1.00	
Treatment group	TACE	1.06 (0.61–1.83)	0.8422	–	0.75 (0.37–1.52)	0.4286
	Y90	1.00			1.00	
Number or LDT	1	0.82 (0.47–1.44)	0.4891	–	0.90 (0.47–1.72)	0.7447
	> 1	1.00			1.00	
Pre-transplant AFP[a]	≤13 ng/mL	0.53 (0.29–0.96)	**0.0463**	0.4167	0.65 (0.33–1.27)	0.2076
	> 13 ng/mL	1.00			1.00	
Pre-transplant UNOS stage[a]	≤T2	0.53 (0.27–1.05)	**0.0360**	0.3240	0.68 (0.33–1.37)	0.2804
	> T2	1.00			1.00	

[a] Univariate analysis on pre-transplant AFP production and UNOS stage was conducted on 155 patients, as pre-transplant AFP values or UNOS stage were not available.
[b] Adjusted for multiple comparison (Bonferroni correction factor = 9).
[c] Multivariate analysis, including all variables used in the univariate analysis, was conducted on 149 patients due to missing values in pre-transplant AFP or UNOS stage. Statistical significance was set at $p < 0.05$.

baseline bilobar disease and pre-OLT AFP > 13 ng/mL. RFS was found to be shorter in cases of baseline bilobar disease [univariate: $p < 0.01$, multivariate: $p = 0.0947$ (trend)] (Table 4).

4. Discussion

4.1. Baseline characteristics

A majority of transplanted patients were treated by TACE or Y90 for very early/early (RFA being considered inappropriate after discussion in the institutional multidisciplinary HCC conference) or intermediate stage HCC (BCLC B). Few patients with PVT (therefore categorized UNOS T4b and BCLC C) were treated by Y90 and subsequently underwent OLT. None of PVT patients were treated with TACE. As evidenced in some studies, Y90 has been reported to show efficacy in treatment of HCC with PVT [12,27,28]. UNOS stage, CP class and BCLC stage were not found to be significantly different between the two treatment groups. Hence, baseline patient characteristics and liver functions were not statistically different between treatment groups [29]. Although not statistically significant, the Y90 group had more patients with advanced HCC given more number of patients with PVT.

4.2. Pre-transplant status

More patients in the TACE group received segmental treatment when compared to the Y90 group. This may suggest that the Y90 group had disease that was not amenable to more selective LDT. There were more treatment sessions in the TACE group when compared to the Y90 group.

In both treatment groups, at least a cytostatic effect was obtained by the LDT (decrease in AFP, bridging/downstaging) [30,31]. Looking at UNOS staging criteria, downstaging from T2 to T1 was likely attributed to a decrease in maximal size of single lesions from > 2 cm to ≤2 cm. Additionally, UNOS staging was performed using measurement of the whole tumor which may underestimate actual response to therapy which should take into account necrosis and enhancement patterns as recommended by the mRECIST guidelines [32]. Using enhancement criteria, downstaging would be more impressive, particularly for downstaging from T3 to T2 [33,34].

4.3. Downstaging of tumors beyond Milan criteria

Although many centers have embraced the practice downstaging tumors by LDTs to fit within regional criteria, clinical practice is still variable. Criteria for assessing tumor response to downstaging therapy and determining eligibility for liver transplantation have been proposed. The proposal anticipated that tumor response to down-staging treatments should be based on radiological measurements of the sizes of viable tumors, and the measurement should exclude the areas of necrosis resulting from locoregional therapy [33]. However, the lack of universal agreement regarding the optimal method for downstaging, selection criteria, and whether or how this should impact on prioritization for a graft represents a challenge for establishing a universal downstaging protocol. In a systematic review of 13 studies (950 patients), success rate for downstaging was 48% (95% CI 39–58%), there was no significant difference between TACE and Y90 [35]. Our results show that 64% of transplanted T3 pre-Y90 patients were successfully downstaged to T2 or less, while 57% of T3 pre-TACE patients were downstaged ($p = 1$). However, selection bias limits the validity of this observation.

4.4. Post-transplant outcomes

No difference was observed in RFS and OS between TACE and Y90 groups, meaning that the local tumor control post-OLT and the systemic toxicity of both techniques could be considered equivalent. HCC recurrence post-OLT was associated with shorter OS. However, a statistically significant effect was not observed, probably because the incidence of recurrence and the follow-up period was limited: 6/79 (8%) in the TACE group and 8/93 (9%) in the Y90 group. The median follow up post-OLT was 26.1 months (IQR: 11.1–49.7).

4.5. Factors predictive of RFS

Bilobar distribution of HCC at baseline was found to be predictive of shorter RFS [36,37]. Distribution could reflect tumor biology and may play a role in imaging strategies for recurrence.

4.6. Role of liver directed therapies

While the role of LDTS in bridging to liver transplantation needs more investigation, there is a trend in clinical practice towards LDTs to maintain patients on the transplant waiting list and reduce the rate of drop-outs while waiting for organs. Current guidelines recommend the use of LDTs especially in patients with expected waiting time exceeding 6 months [7]. There are no recommendations for a specific LDT of choice over another. Comparative studies between Y90 and TACE showed similar survival outcomes. A randomized controlled trial showed advantage of Y90 over TACE with a TTP for Y90 cohort exceeding 26 months vs. 6.8 months for TACE cohort ($p = 0.0012$) [21]. This would certainly benefit transplant candidates by preventing them from dropping-out of the transplant waiting list. Other LDTs include DEB-TACE, with promising results in terms of TTP and tumor necrosis [38,39]. However, when compared with conventional TACE, there was no statistically significant difference in overall survival after OLT, with a tendency towards better RFS in DEB-TACE cohort [40]. Most recently, a randomized controlled trial, comparing DEB TACE to embolization with microsphere alone showed no significant difference in overall survival and progression free survival between two arms [41].

4.7. Strengths and limitations

This is the first clinical study focusing on post-OLT outcome after TACE or Y90. The concept of bridging and downstaging to OLT was also evaluated by imaging (UNOS) and biological metrics (AFP). The number of patients and the follow-up period was acceptable for a survival study but limited for the interpretation of the multivariate analysis. We recognize the limitation inherent to the selection bias of analyzing only transplanted patients, those exhibiting favorable biology and response. There were patients who underwent OLT despite not meeting UNOS transplant criteria (T3, T4a, and T4b); this likely represents variability in radiological interpretation. While we followed standard of care imaging frequency in transplanted patients, these are often not as intensive as q3 month images obtained during the active management period of patients with cancer. The etiology of death was undetermined for some patients (lost to follow-up with known date of death). Finally, the outcome post-OLT was not compared to an untreated population or undergoing other techniques such as RFA.

4.8. Future perspectives

Future clinical studies on post-OLT outcome should be conducted in a prospective fashion with adapted HCC recurrence screening protocols (frequent and extensive work up). On the other hand, treatment options of recurrent HCC post-OLT and their efficacy is still to be determined. Attention should also be turned on biochemical and clinical mechanisms present in the pathogenesis of HCC recurrence to improve prognosis of recurrence and on early markers of recurrence (serum biomarkers, blood circulating tumor cells, imaging criteria, etc.). Finally, treatment options for HCC recurrence after OLT should be investigated. For instance, extra-hepatic recurrence would open candidacy to systemic therapy versus best supportive care. However, intrahepatic recurrence may behave differently; should listing for a second OLT be considered, or should BCLC recommendations be applied to HCC recurrence? There is a need for more robust and uniform HCC screening in this select group of patients. Hopefully, with a better understanding of the disease, post-transplant outcomes and treatment efficacy, guidelines of post-OLT HCC recurrence management and comprehensive algorithms could be proposed in the near future.

5. Conclusion

Our analysis focuses on 172 post-OLT patients who had received pre-transplant transarterial LDTs for HCC. Despite longer time-to-OLT for Y90, post-OLT outcomes were similar between patients with HCC bridged or downstaged by TACE or Y90, supporting the use of Y90 as a bridging or downstaging option in HCC.

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Conflict of interest

RJL, LK, and RS are advisors to BTG. Other authors report no conflict of interest.

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