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INTERVENTIONAL RADIOLOGY

ORIGINAL ARTICLE

Does neoadjuvant doxorubicin drug-eluting bead transarterial chemoembolization improve survival in patients undergoing liver transplant for hepatocellular carcinoma?

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PURPOSE
We aimed to compare the overall (OS) and disease-free survival (DFS) of patients undergoing orthotopic liver transplant (OLT) for hepatocellular carcinoma who did and did not have neoadjuvant doxorubicin drug-eluting bead transarterial chemoembolization (DEB-TACE).

METHODS
This is a retrospective study of 94 patients with HCC transplanted between 2000 and 2014 in a single tertiary center. Pre- and postoperative features, DFS and OS were compared between patients who received pre-OLT DEB-TACE (n=34, DEB-TACE group) and those who did not (n=60, non-TACE group). Radiologic and histologic response to neoadjuvant treatment as well as its complications were also studied.

RESULTS
There were no significant differences in post-transplantation DFS and OS rates between groups (5-year DFS: 70% in DEB-TACE group vs. 63% in non-TACE group, $P = 0.454$; 5-year OS: 70% in DEB-TACE group vs. 65% in non-TACE group, $P = 0.532$). The DEB-TACE group had longer OLT waiting time compared with the non-TACE group (110 vs. 72 days; $P = 0.01$). On univariate and multivariate analyses, alpha-fetoprotein (AFP) levels >500 ng/mL prior to OLT were associated with decreased OS and DFS regardless of neoadjuvant approach (hazard ratio of 6, $P = 0.001$ and 5.5, $P = 0.002$, respectively).

CONCLUSION
Patients who underwent neoadjuvant DEB-TACE and OLT for hepatocellular carcinoma had no statistically different OS or DFS at 3 and 5 years from patients undergoing OLT alone.

Orthotopic liver transplant is the gold standard treatment for patients with hepatocellular carcinoma (HCC) within Milan criteria (1, 2). Conventional transarterial chemoembolization (cTACE) is widely accepted as a palliative treatment for patients who do not fulfill the criteria for OLT, HCC resection, or local therapies such as ethanol injection, radiofrequency ablation, microwave ablation, cryotherapy, or electroporation (3–11). The usefulness of pre-OLT TACE to avoid disease progression while waiting for organ allocation and to down-stage selected patients to fulfill transplant criteria is well known. However, the effect of neoadjuvant TACE treatment prior to OLT for HCC on overall survival (OS) and disease-free survival (DFS) is contentious (2, 12–22).

Doxorubicin drug-eluting bead TACE (DEB-TACE) is a drug delivery embolization system that can achieve higher tumor and lower systemic concentrations of doxorubicin compared with cTACE and demonstrated equal efficacy with low toxicity in previous clinical studies (23–27). However, the evidence to support the use of this relatively novel technique as a neoadjuvant treatment before OLT and its impact on OS and DFS is scarce.

The aim of this study was to compare OS and DFS of patient undergoing OLT for HCC who did and did not receive neoadjuvant DEB-TACE.

Methods

Study design and population

Data was investigated from a prospectively maintained database and the need to ob-

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tain informed consent was waived. The research was performed according to the World Medical Association Declaration of Helsinki.

This is a retrospective study of all patients diagnosed with HCC (either radiologically and/or by percutaneous biopsy, in accordance with the American and European Association for the Study of Liver Disease guidelines) (28, 29) who underwent OLT as a curative treatment between September 2000 and November 2014. Patients initially listed for OLT but dropped from the list for any reason, patients who underwent neoadjuvant treatment other than DEB-TACE (including cTACE), and patients diagnosed with incidental HCC on final histopathology report were excluded from the study.

Patients were added to the liver transplant waiting list on the basis of a multidisciplinary team decision, in accordance with international guidelines (2, 28, 29) based on the patient fulfilling Milan criteria or their expansion (1, 30). Since 2002, once on the OLT waiting list, HCC patients were prioritized by receiving 21 Model for End Stage Liver Disease (MELD) exception points (31).

Study group

Of a total of 116 patients listed for OLT following a diagnosis of HCC during the study period, 100 patients underwent OLT. Transplantation was preceded by DEB-TACE in 34 cases, while the rest did not have chemoembolization (non-TACE). In total, 10 patients (6 DEB-TACE and 4 non-TACE; $P = 0.121$) were dropped from the waiting list due to disease progression and 6 patients for other reasons (abstinence from alcohol incompliance or acute liver failure leading to death). Additionally, 6 patients were excluded from the study because they received neoadjuvant local treatment other than DEB-TACE (4 radiofrequency ablations and 2 cTACE). Therefore 94 patients (34 DEB-TACE and 60 non-TACE) were included in the study.

Main points

- Neoadjuvant doxorubicin drug-eluting bead transarterial chemoembolization (DEB-TACE) does not improve survival in hepatocellular carcinoma patients with a waiting list time of <6 months for liver transplantation.
- Pretransplantation alpha-fetoprotein level of >500 ng/mL is a risk factor for decreased overall and disease-free survival.
- Randomized clinical trials comparing the survival rates of patients who did and did not receive neoadjuvant DEB-TACE are needed.

Preoperative treatment

Neoadjuvant DEB-TACE for HCC patients awaiting OLT was first employed in our institution in 2006. From 2006 to 2014, as international consensus based protocols to guide the use of neoadjuvant DEB-TACE were lacking, patients were selected to undergo preoperative DEB-TACE on a case by case basis. This decision was undertaken by a multidisciplinary team and was based on a number of factors including the expected time on transplantation waiting list (primarily dependent upon the MELD score, blood group, and weight) and on disease characteristics such as number and size of tumors.

Pre-TACE evaluation included review of medical history, physical examination, and laboratory studies for hematologic, hepatic, and renal functions along with serum alpha-fetoprotein (AFP). The imaging workup consisted of a baseline contrast-material enhanced computed tomography (CT) or magnetic resonance imaging (MRI) within 1 month preceding the DEB-TACE procedure. DEB-TACE was repeated until angiographic response was expected.

Following DEB-TACE, if transplantation did not occur first, patients underwent interim contrast-enhanced MRI or CT to assess DEB-TACE tumor response, 4 to 8 weeks after the procedure. Response to therapy was assessed on imaging using modified RECIST criteria (32) and EASL criteria (29). DEB-TACE was then repeated, at 4–8 weeks interval, until a complete response was achieved or a donor organ became available. In patients with a complete radiologic response, a CT or MRI study was repeated every 4 months and AFP levels were tested every 2 months whilst the patient remained on the waiting list.

DEB-TACE procedure

Informed consent was obtained from all patients before the procedure. All patients were premedicated with antibiotics (cefuroxime 750 mg and metronidazole 500 mg, intravenously). Either 100–300 µm or 300–500 µm DC Beads™ (AngioDynamics) were used for embolization. A total of 4 mL of microspheres were mixed with 150 mg doxorubicin according the manufacturer's guidelines. Patients received conscious sedation during the procedure using fentanyl and midazolam. Blood pressure, oxygen saturation, electrocardiographic parameters, and heart rate were monitored during the entire procedure. Femoral arterial access was used in all patients. Celiac and/or superior mesenteric arteriography was performed to assess the arterial anatomy, vascular supply to the tumor, and patency of the portal vein. The lobar/segmental hepatic artery supplying the tumor was selectively cannulated with a microcatheter and embolized with drug-eluting microspheres, which were mixed with nonionic iodinated contrast material in a ratio of 1:5. The endpoint for embolization was stasis of blood flow in the arterial feeders to the tumor. A search with additional angiography was made for detection of extrahepatic arterial supply to the tumor. If the extrahepatic artery was suitable for embolization, the artery was selectively cannulated and embolized with drug-eluting microspheres.

Patients were admitted for observation for 24 hours following the procedure. Prophylactic medications against nausea (intravenous ondansetron) and pain and intravascular hydration were administered during hospitalization. Safety of DEB-TACE was assessed by calculating incidence of postprocedure complications according to Society of Interventional Radiology (SIR) guidelines (33) and the Dindo-Clavien classification (34). The incidence of postprocedure liver failure, renal failure, or death within 30 days of the procedure was also calculated. Biochemical toxicity was assessed using National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 (35).

Postoperative follow-up

Post-OLT follow-up was based on current international recommendations (2). Patients underwent CT or MRI scanning and AFP measurement every 6 months during the first 2 years and additional imaging techniques were performed if HCC recurrence was suspected.

Data analysis

Primary outcomes were post-OLT OS and DFS; secondary outcomes were post-TACE morbidity, length of stay, radiologic and histologic response, postoperative graft loss, hepatic artery thrombosis, and mortality within 30 days.

Distribution of continuous variables' was determined using Kolmogorov-Smirnov test and expressed as mean ± standard deviation or median and range. Categorical variables were compared using chi-square

test or Fisher exact test, as appropriate. Continuous data were compared using independent samples t-test or its nonparametric analogue. Survival time was calculated from the date of OLT to the date of the event of interest (death for OS, relapse for DFS) or the date of the last follow-up. To estimate DFS, patients without evidence of recurrence were censored at the time of last follow-up or death. Patient OS and DFS were estimated using Kaplan-Meier method and these curves were compared with log-rank tests. Multivariate analysis using a Cox multiple stepwise regression model was performed to evaluate the influence of different variables on OS and DFS. Data collection and analyses were performed with Statistical Package for the Social Sciences (version 16.0; SPSS Inc.). $P < 0.05$ was considered significant.

Results

Demographic and preoperative data of the DEB-TACE and non-TACE groups, obtained just before OLT, are depicted in Table 1.

Patients who underwent DEB-TACE had a significantly longer waiting time for transplantation (110 vs. 72 days; $P = 0.005$) and had a lower MELD score (10 vs. 13; $P = 0.019$) than non-TACE patients. No intergroup differences were observed in gender, age, albumin level, etiology, AFP levels at diagnosis or prior to transplantation, number of nodules, and cumulative and maximum tumor diameter.

A total of 47 DEB-TACE procedures were performed on 34 patients. No patients died within 30 days of DEB-TACE procedures. No patients had major complications after DEB-TACE (Clavien grade 1: n=2 (4%), no complications: n=45 (96%); SIR grade A: n=2 (4%), no complications: n=45 (96%); no postprocedure acute liver or kidney failure was observed). The median length of stay after DEB-TACE was 1 day (range, 1–15). Only three patients had a length of stay of more than 3 days. The reason for prolonged stays was pre-OLT work-up in all cases.

Radiologic follow-up of DEB-TACE was available in 36 procedures and showed stable disease in 4 cases (11%), partial response in 24 cases (67%), and complete radiological response in 8 cases (22%). Eleven patients (11%) received OLT before the first post-TACE radiologic follow-up. No difference in OS and DFS was observed between complete radiologic responders and non-complete radiologic responders (data not shown) among DEB-TACE patients. Five patients did not fulfill Milan criteria and were down-staged by one or more DEB-TACE sessions.

The histopathology report and early postoperative results for the two groups are shown in Table 2. Histopathologic assessment of the necrosis achieved by DEB-TACE in the explanted liver tumor was available in 20 of the 34 treated patients (59%) and 7 (35%) of them showed a complete pathologic response to neoadjuvant treatment. However, there was no difference in DFS or OS between this complete response subgroup and the remaining DEB-TACE patients (data not shown).

There were no differences in postoperative length of hospital admission, hepatic artery thrombosis, 30-day graft loss, and 30-day mortality between the DEB-TACE and non-TACE groups (Table 2).

Mean follow-up after OLT was 47±39 months (29±23 months and 57±42 months in DEB-TACE and non-TACE groups, respectively). Overall 4 DEB-TACE (12%) and 7 non-TACE (12%) patients had disease recurrence

Table 1. Demographic and preoperative data of DEB-TACE and non-TACE groups

	DEB-TACE (n=34)	Non-TACE (n=60)	*P*
Male, n (%)	28 (82)	51	0.743
Age, years (mean±SD)	60±9	56±9	0.121
MELD score (mean±SD)	10±4	13±5	0.005*
Albumin (mean±SD)	34±11	32±6	0.465
Ascites, n (%)	4 (12)	15	0.098
Alcohol, n (%)	9 (26)	16	0.987
HCV, n (%)	12 (35)	19	0.719
HBV, n (%)	3 (9)	4	0.763
Other etiologies, n (%)	10 (29)	21	0.576
AFP at diagnosis, ng/mL (median, range)	5 (1–7568)	5 (1–889)	0.954
AFP before OLT, ng/mL (median, range)	4 (1–7568)	5 (1–889)	0.821
Number of nodules (mean±SD)	1.4±0.8	1.4±0.8	0.965
Maximum diameter, mm (mean±SD)	32±14	28±9	0.165
Cumulative diameter, mm (mean±SD)	38±19	35±16	0.365
Waiting list, days (mean±SD)	110±84	72± 65	0.019*
Patients waiting >6 months, n (%)	8 (23)	2 (3)	0.003*

* $P < 0.05$.
DEB-TACE, doxorubicin drug-eluting bead transarterial chemoembolization; Non-TACE, no transarterial chemoembolization before liver transplantation; SD, standard deviation; MELD, model for end stage liver disease; HCV, Hepatitis C virus; HBV, Hepatitis B virus; AFP, alpha-fetoprotein; OLT, orthotopic liver transplantation.

Table 2. Comparison of the early postoperative data and histopathologic examination results between DEB-TACE and non-TACE groups

	DEB-TACE (n=34)	Non-TACE (n=60)	
	n (%)	n (%)	*P*
Inside Milan criteria confirmed by HPR	30 (88)	46 (77)	0.176
TNM stage 1	13 (46)	34 (57)	0.376
Histologic grade 1	22 (65)	39 (52)	0.919
Microvascular invasion	7 (23)	20 (33)	0.365
HAT	1 (3)	2 (3)	0.898
30-day graft loss	1 (3)	6 (10)	0.219
30-day mortality	1 (3)	7 (12)	0.143

DEB-TACE, doxorubicin drug-eluting bead transarterial chemoembolization; Non-TACE, no transarterial chemoembolization before liver transplantation; HPR, histopathology report; HAT, hepatic artery thrombosis.

Table 3. Univariate analysis for overall survival and disease-free survival on the entire cohort of patients (n=94)

	3-year OS %	5-year OS %	*P*	3-year DFS %	5-year DFS %	*P*
Male	77	70	0.265	75	68	0.187
Female	61	51		60	50	
Age >60 years	70	56	0.821	69	56	0.865
Age <60 years	78	75		76	72	
Ascites	77	76	0.421	76	76	0.354
No ascites	78	67		75	65	
Cumulative diameter >30 mm	80	73	0.476	79	70	0.463
Cumulative diameter <30 mm	72	60		68	53	
Outside Milan criteria	74	66	0.919	72	66	0.874
Inside Milan criteria	92	81		91	69	
Nodule number >1	88	79	0.365	87	60	0.365
Nodule number <1	73	65		71	66	
DEB-TACE	79	70	0.532	79	70	0.454
Non-TACE	73	65		70	63	
Max nodule diameter >30 mm	80	76	0.532	79	71	0.521
Max nodule diameter <30 mm	72	60		69	60	
Vascular invasion	68	68	0.776	68	61	0.854
No vascular invasion	77	65		75	65	
TNM stage >1	74	57	0.643	71	56	0.687
TNM stage <1	72	72		72	72	
Histologic grade >1	73	63	0.221	70	60	0.221
Histologic grade <1	70	64		70	63	
AFP OLT >500 ng/mL	33	33	0.007*	33	33	0.019*
AFP OLT <500 ng/mL	79	71		77	69	

* $P < 0.05$.
OS, overall survival; DFS, disease-free survival; DEB-TACE, doxorubicin drug-eluting bead transarterial chemoembolization; Non-TACE, no transarterial chemoembolization before liver transplantation; AFP, alpha-fetoprotein; OLT, orthotopic liver transplantation.

Table 4. Multivariate analysis for overall survival and disease-free survival on the entire cohort of patients (n=94)

	OS HR	*P*	DFS HR	*P*
Male	0.6	0.432	0.5	0.354
Age >60 years	1.6	0.354	1.5	0.343
Ascites	0.7	0.776	0.7	0.654
Cumulative diameter >30 mm	1.1	0.932	0.9	0.987
Inside Milan criteria	0.5	0.476	0.6	0.653
Nodule number >1	0.4	0.532	0.5	0.598
DEB-TACE	1.9	0.298	1.8	0.365
Max nodule diameter >30 mm	1	0.954	1.2	0.876
Vascular invasion	0.5	0.376	0.5	0.421
TNM stage >1	1.6	0.443	1.5	0.521
Histologic grade >1	0.4	0.221	0.5	0.219
AFP OLT >500 ng/mL	6	0.019*	5.5	0.021*

* $P < 0.05$.
OS, overall survival; HR, hazard ratio; DFS, disease-free survival; DEB-TACE, doxorubicin drug-eluting bead transarterial chemoembolization; AFP, alpha-fetoprotein; OLT, orthotopic liver transplantation.

during the study period. There was no difference between 3-year and 5-year OS and DFS rates as depicted in Figs. 1 and 2 (3-year OS: 79% in DEB-TACE group vs. 73% in non-TACE group; 5-year OS: 70% in DEB-TACE group vs. 65% in non-TACE group; 3-year DFS: 79% in DEB-TACE group vs. 70% in non-TACE group; 5-year DFS, 70% in DEB-TACE group vs. 63% in non-TACE group).

On univariate analysis only pretransplantation AFP levels >500 ng/mL correlated significantly with OS and DFS (Table 3). No other variable was found to influence OS and DFS rates, including Milan criteria compliance, the number of nodules, the cumulative tumor diameter, the histologic grade and the use of DEB-TACE as perioperative treatment (Table 3). These findings were confirmed by multivariate analysis, where only pretransplantation AFP levels >500 ng/mL increased the risk of death or recurrence with a hazard ratio of 6 and 5.5 respectively in the entire cohort (Table 4).

Discussion

DEB-TACE has been shown to be safe and effective in palliative HCC treatment in several clinical and preclinical studies (27, 36–41), as well as in a randomized clinical trial (RCT) comparing DEB-TACE with cTACE (23, 26), but the evidence to support its use as a neoadjuvant treatment before OLT is scarce (25, 42–46). To our knowledge, this is the first clinical study that compares OS and DFS of patients that did and did not receive DEB-TACE before OLT and one of the largest series assessing neoadjuvant DEB-TACE clinical results in the literature so far.

The use of cTACE prior to resection of HCC has been examined in 3 RCTs, universally yielding negative results in terms of OS and DFS (47–49). One such study, published by Zhou et al. (47) delineated the negative impact of preoperative cTACE on a range of parameters including post-cTACE complications, impairment of liver function and increased technical difficulty for future transarterial treatments. Furthermore, the author expressed concerns regarding the potentially deleterious outcome of partial tumor necrosis induced by neoadjuvant cTACE, which could cause dislodgement of remaining tumor cells into the bloodstream. The authors concluded that preoperative cTACE cannot be recommended for resectable HCC. In the current study, patients treated by neoadjuvant DEB-TACE had no postprocedure deaths or severe complications. Furthermore, no evidence of

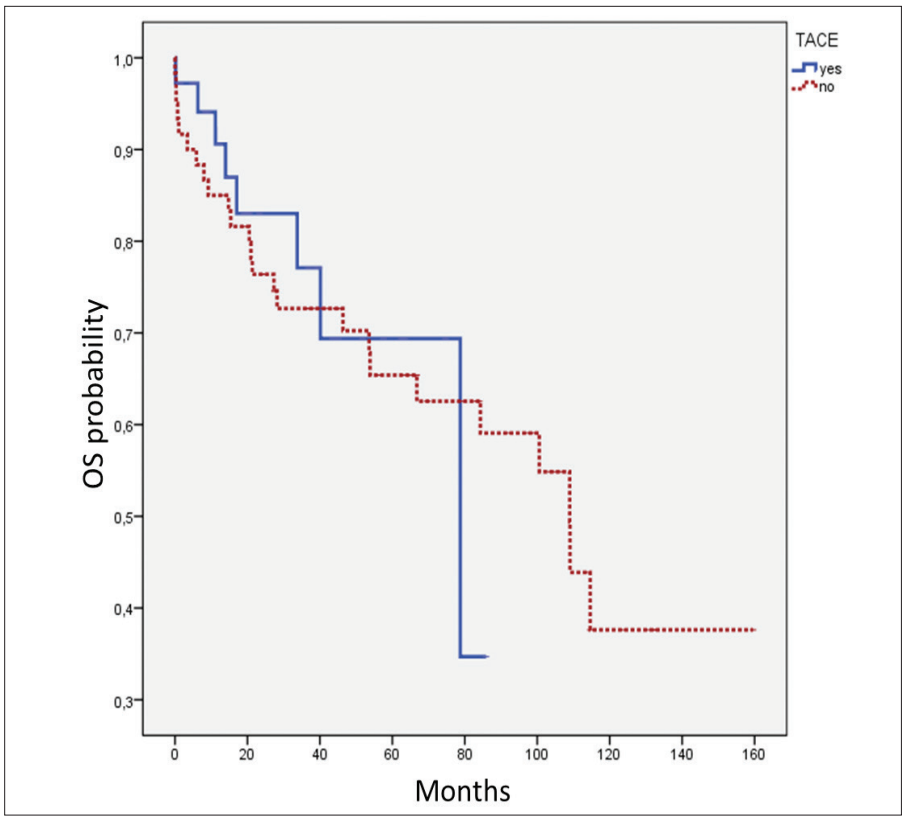

Figure 1. Kaplan-Meier overall survival (OS) curves for patients who did and did not have doxorubicin drug-eluting bead transarterial chemoembolization (DEB-TACE) before orthotopic liver transplantation.

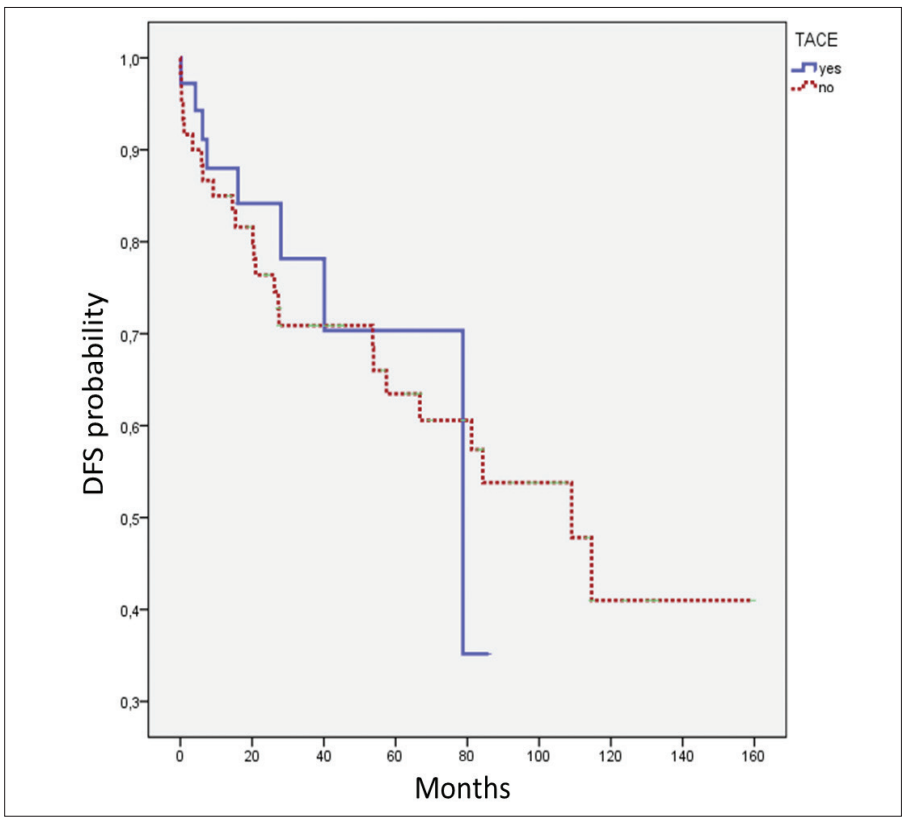

Figure 2. Kaplan-Meier disease-free survival (DFS) curves for patients who did and did not have doxorubicin drug-eluting bead transarterial chemoembolization (DEB-TACE) before orthotopic liver transplantation.

altered OS or DFS when comparing patients with DEB-TACE and complete response with patients with stable disease or partial pathological was observed.

The rationale for the use of TACE prior to OLT is multifaceted. Firstly, the goal is to avoid tumor progression while patients await allocation of a donor organ, particularly if this waiting period is expected to be in excess of 6 months (2, 50). Secondly, TACE is theorized to have the potential to downstage patients outside transplantation selection criteria (51) and thirdly to increase OS and DFS after OLT. However, the current indication for TACE as a bridging therapy before OLT is based only on retrospective series (2) and there are no available RCTs to support the use of neoadjuvant DEB-TACE or cTACE before OLT. In our experience, patients diagnosed with HCC who received neoadjuvant DEB-TACE before OLT have the same OS and DFS as those who had OLT alone. These findings agree with several previous nonrandomized studies evaluating the use of neoadjuvant cTACE (14, 17–19, 21, 22). However, comprehensive review of the literature reveals no overall consensus on the survival benefit of neoadjuvant cTACE, with many studies equivocal and conflicting (2, 12–22). In the current study, the effectiveness of DEB-TACE to down-stage patients to fulfill OLT criteria and to prevent dropouts from the waiting list was not under evaluation. Our aim was to evaluate the effect of DEB-TACE on OS and DFS after OLT. Intention-to-treat analysis was, therefore, not performed, and patients dropped from OLT list were excluded from the study.

The relatively low number of patients in each subgroup, as well as the retrospective nature of the study represents a weakness of our work. Selection bias cannot be totally avoided in retrospective studies. In our series DEB-TACE patients had a significantly longer waiting list time (110 vs. 72 days) and lower MELD score. The waiting list time is one of the selection criteria for patients to undergo preoperative DEB-TACE and also represents a risk factor for tumor progression while waiting for OLT. Furthermore, we are aware that only a small number of our patients in both groups waited over 6 months and that rapid transplantation may have impacted our results in favor of no effect of DEB-TACE.

In conclusion, patients who underwent neoadjuvant DEB-TACE and OLT for HCC had the same OS or DFS at 3 and 5 years

as patients undergoing OLT alone, despite longer waiting list time. However, neoadjuvant DEB-TACE is a safe procedure, does not compromise subsequent OLT and does not increase post-OLT complications rates, as previously reported by others authors (52). The results of the current work suggest that in a population with a waiting list of <6 months, neoadjuvant DEB-TACE has no survival benefits. Future RCTs are needed to demonstrate the oncologic benefit of DEB-TACE on this subgroup of patients and in down-staging of HCC patients outside the OLT criteria.

Conflict of interest disclosure

The authors declared no conflicts of interest.

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