

Deceased Donor Liver Transplantation After Radioembolization for Hepatocellular Carcinoma and Portal Vein Tumoral Thrombosis: A Pilot Study

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Hepatocellular carcinoma (HCC) with portal vein tumoral thrombosis (PVTT) represents a major concern especially in the field of deceased donor liver transplantation (DDLT). However, when receiving transarterial radioembolization (TARE), a considerable percentage of such patients are able to achieve a radiologic complete response with adequate survival rates. In this pilot prospective study, we evaluated the effect of TARE in downstaging HCC patients with PVTT to meet criteria for DDLT. Between May 2013 and November 2016, patients were evaluated to be enrolled into our “Superdownstaging” protocol. Patients received yttrium-90 TARE and were enlisted for DDLT in case of complete and sustained (6 months) radiological response. Patients with tumor thrombus in the main trunk and/or in the contralateral portal vein branch were excluded. TARE was effective in downstaging and receiving DDLT in 5/17 patients (29.4%). The 5-year overall survival was significantly higher in patients who underwent DDLT compared with those who were not transplanted (60.0% versus 0.0%, $P = 0.03$). Three out of 5 patients developed recurrence within 1 year after LT. The current series showed a clear survival gain in those patients who were able to receive DDLT after TARE but careful selection for DDLT is however advised.

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Hepatocellular carcinoma (HCC) is the second most frequent cause of cancer-related death worldwide.

Abbreviations: AASLD, American Association for the Study of Liver Diseases; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; CP, Child-Pugh; CR, complete response; CT, computer tomography; CTCAE, Common Terminology Criteria for Adverse Events; DDLT, deceased donor liver transplantation; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; IQR, interquartile range; ITT, intention -to -treat; LDLT, living

Both European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) guidelines for the treatment of HCC endorse the Barcelona Clinic Liver Cancer (BCLC) classification.⁽¹⁻³⁾ Liver transplantation (LT) is indicated in the early stage of BCLC (0-A) because the presence of advanced cancer correlates with poor posttransplantation survival. Patients with HCC and portal vein tumoral thrombosis (PVTT) are classified as BCLC C, but they can be, in selected cases, referred to surgeons for resectability assessment.⁽⁴⁾ However most of these patients require extensive hepatectomies, often impossible to perform due to the

underlying cirrhosis. In these patients, sorafenib represents the treatment of choice,⁽⁵⁾ but more recently, transarterial radioembolization (TARE) with yttrium-90 has been also proposed. With the increasing evidence supported by the recent literature, a considerable percentage of such patients are not only able to achieve stability of the disease, but also to obtain a radiologic complete response (CR).^(6,7) At present, however, no further treatment is recommended and only few cases have been reported in the field of living donor LT (LDLT). The possibility of achieving a CR might allow these patients to be listed also for deceased donor LT (DDLT),⁽⁸⁾ according to the principle of transplant benefit.⁽⁹⁾

The primary endpoint of this study was to assess the effect of TARE in downstaging patients with HCC having PVTT according to our “Superdownstaging” protocol, allowing them to become eligible for DDLT. The secondary endpoints were overall survival (OS) and progression-free survival (PFS). We also compared OS and PFS between the transplanted group and the nontransplanted group.

donor liver transplantation; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; MRI, magnetic resonance imaging; mRECIST, modified Response Evaluation Criteria in Solid Tumors; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PVTT, portal vein tumoral thrombosis; TACE, transarterial chemoembolization; TARE, transarterial radioembolization.

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The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

**These authors share the first authorship.*

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Patients and Methods

STUDY POPULATION

All patients diagnosed with HCC and PVTT between May 2013 and November 2016 were evaluated to be enrolled into our “Superdownstaging” protocol. Inclusion criteria were (1) diagnosis of HCC according to EASL and AASLD criteria^(2,3); (2) aged 18 years or older; (3) Eastern Cooperative Oncology Group performance status of 0-1; (4) preserved liver function (Child-Pugh [CP] score \leq B7); (5) PVTT limited to the first-order portal branch. Exclusion criteria were (1) any contraindication to TARE treatment; (2) macrovascular invasion extended to the main portal trunk and/or to the contralateral portal branch; (3) presence of extrahepatic disease.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in a priori approval by the institution's human research committee. Informed consent was obtained from each patient included in the study, and the institutional review board gave ethical approval to perform this study (#45/2015/O/Oss). The study protocol was registered on ClinicalTrials.gov (identifier NCT04771988).

STUDY DESIGN

Patients aged 18-65 years presenting with advanced HCC at our institution were eligible for inclusion. TARE was proposed with an intention to downstage to within Milan Criteria.⁽¹⁰⁾ The decision of downstaging was taken by a multidisciplinary team comprising interventional radiologists, hepatologists, transplantation surgeons, radiation oncologists, nuclear medicine physicians, and medical physicists. To exclude the presence of extrahepatic metastases, a complete (chest/abdomen/pelvis) radiological evaluation was performed using dynamic and multiphase contrast-enhanced computer tomography (CT) or magnetic resonance imaging (MRI). Whole-body [¹⁸F]fludeoxyglucose PET/CT scan and bone scintigraphy were not available for every patient. Patients who underwent TARE were monitored with a clinical, radiological, and laboratory follow-up at 1, 3, and 6 months and then every 3 months from the initial treatment, in accordance with the current practice adopted by our institution. The overall response to TARE was assessed according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria.⁽¹¹⁾ After a multidisciplinary board decision, the patient was enlisted for LT according to our previously described criteria⁽¹²⁾ and

in particular in case of (1) complete (ie, disappearance of PVTT enhancement on cross-sectional imaging) and sustained (6 months after TARE) radiological response of PVTT; (2) successful downstaging of HCC to within Milan Criteria; (3) alpha-fetoprotein (AFP) less than 100 ng/mL (Fig. 1). Restaging of disease was performed every 3 months before LT by means of blood tests, AFP, chest CT, and abdominal contrast-enhanced CT scan (or MRI). After LT, patients were screened for tumor recurrence every 3 months up to the first postoperative year, then at least every 6 months. Immunosuppressive therapy consisted of tacrolimus and a steroid taper according to standard practice at our center.

TARE PROCEDURE

TARE was performed using resin microspheres labeled with yttrium-90 (SIR-Spheres; Sirtex Medical, Sydney, Australia). The pretreatment workup included an angiographic study of the liver and tumor vascularization and a therapy simulation of the treatment using technetium-99m-labeled macroaggregated albumin both to detect on the single-photon emission computed tomography-CT images all collateral vessels that may carry microspheres to extrahepatic organs and to rule out the lung shunt.⁽¹³⁾ Patients received a selective/supers elective treatment depending on the distribution of tumor burden and hepatic vasculature. The activity of yttrium-90-loaded microspheres to be injected was calculated using the Medical Internal Radiation Dosimetry formalism called the “partition model.” The Medical Internal Radiation Dosimetry formalism is based on

the determination of the fraction of activity (fractional uptake) that is trapped by the tumor, by the normal liver and the lungs, and by the volume of each liver segment which is calculated using CT images. The fractional uptake was determined using technetium-99m-labeled macroaggregated albumin single-photon emission computed tomography images. The day after TARE, a yttrium-90 PET/CT study was performed to visually assess microspheres distribution and to calculate the mean dose to target, liver, and lungs based on the partition model. The nature and severity of all adverse events were recorded from the medical records and graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

VARIABLES

The following variables were collected: demographics (sex, age, etiology of underlying liver disease), laboratory (total bilirubin, serum albumin, international normalized ratio, AFP), size and number of HCC nodules, other locoregional treatments, and explant pathology findings including the presence of residual PVTT. Liver function was evaluated according to the CP⁽¹⁴⁾ and the albumin-bilirubin scores.⁽¹⁵⁾ PVTT was diagnosed as intrathrombus vascularity observed in the arterial phase after the administration of contrast on cross-sectional dynamic imaging,⁽¹⁶⁾ and classified according to the Liver Cancer Study Group of Japan⁽¹⁷⁾: Vp1, tumor thrombus in one-third or more of the peripheral branch of the portal vein; Vp2, tumor thrombus in a second branch of the portal vein; Vp3, tumor thrombus in the first branch of the portal vein.

STATISTICAL ANALYSIS

Data were expressed as median and interquartile range (IQR), when appropriate. Mann-Whitney U test was used for comparison of continuous variables and chi-square test or Fisher’s exact test was used for comparisons of categorical variables. OS was calculated from the date of TARE to the death of patient or last follow-up. PFS was defined as the time from TARE to progression of disease, recurrence after LT, or last follow-up without recurrence. Survival rates were calculated using the Kaplan-Meier method and compared using the log-rank test. Analyses were by intention-to-treat (ITT). All statistical tests were 2-tailed, and differences were considered significant at a *P* value of ≤ 0.05 . Data analysis was performed with SPSS version for Windows (IBM, New York, NY).

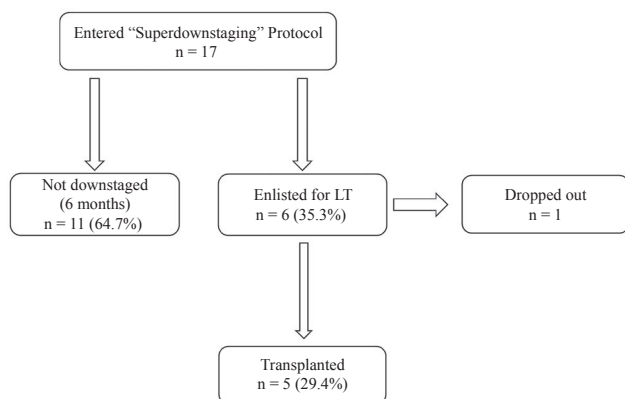


FIG. 1. Flowchart of the study.

Results

During the study period, 17 patients were enrolled. Baseline characteristics of the overall population are shown in Table 1. Median age at the time of TARE was 53 years (range, 50-56 years). There were 15 males and 2 females. According to albumin-bilirubin score, grade 1 and grade 2 were 58.8% and 41.2%, respectively, whereas CP A represented 88.2% of cases. The main cause of cirrhosis was hepatitis C virus infection (70.6%). Out of 17 patients, 6 (35.3%) received different neoadjuvant treatments prior to TARE, with PVTT diagnosed at the time of HCC recurrence in all but 1 case. The median number of HCC nodules at the time of TARE was 1 (IQR, 1-2), whereas the median diameter of the largest lesion was 59 mm (IQR, 43-70 mm). PVTT was classified as follows: Vp1 (n = 3), Vp2 (n = 5), and Vp3 (n = 9). Median AFP was 18.6 ng/mL (IQR, 7.3-103.4 ng/mL).

TARE PROCEDURE

The injected activity; tumor volume; percentage of targeted to total liver volume; lung shunt; mean dose to tumor, liver, and lungs; and the characteristics of the TARE treatment are reported in Table 2. Periprocedural adverse events occurred in 4/17 (23.5%) and consisted of grade 1 abdominal pain in 3 patients, and grade 1 fever and fatigue in 1 patient. In all cases medical therapy was performed. Late complications included mild ascites, occurred in 2/17 patients (11.7%), starting from 15 to 90 days after the treatment and resolved with diuretic therapy in all cases.

ITT OUTCOMES

Three patients showed progression of hepatic disease at 1- and 3-month evaluation respectively, and died within 6 months. The remaining 14 patients could be evaluated at 6 months for LT eligibility (Table 3). Six out of 17 patients (35.3%) showed complete and sustained radiological response of PVTT, and after multidisciplinary discussion, they were enlisted for LT. Among them, a 53-year-old male patient with hepatitis C virus-related liver cirrhosis, after almost 2 years of sustained radiological response, was diagnosed with multiple cardiac metastases on the day of LT, which was detected during transesophageal echocardiography, and therefore did not undergo LT.

TABLE 1. Baseline Characteristics of Patients at TARE Treatment (n = 17)

Variable	Values
Age, years	53 (50-56)
Sex, male/female	15/2
Cirrhosis	17 (100.0)
Platelets, n × 10 ³	92 (75-156)
Albumin-bilirubin score	
Grade 1	10 (58.8)
Grade 2	7 (41.2)
CP score	
A	15 (88.2)
B	2 (11.8)
Etiology of cirrhosis	
Hepatitis C virus	12 (70.6)
Hepatitis B virus	1 (5.9)
Cryptogenetic	1 (5.9)
Nonalcoholic fatty liver disease	3 (17.6)
Number of HCC nodules, count	1 (1-2)
Maximum diameter, mm	59 (43-70)
Tumor burden score ≥50%	0 (0.0)
Tumor morphology	
Infiltrative	12 (70.6)
Nodular	5 (29.4)
Neoadjuvant therapies before TARE	6 (35.3)
Type of neoadjuvant therapies	
TACE	4 (23.5)
Radiofrequency ablation	2 (11.8)
Hepatic resection	3 (17.6)
Chemotherapy	3 (17.6)
AFP, ng/mL	18.6 (7.3-103.4)
AFP ≥100 ng/mL	5 (29.4)
PVTT type	
Vp1	3 (17.6)
Vp2	5 (29.4)
Vp3	9 (53.0)
Milan prognostic score	
Favorable	3 (17.6)
Intermediate	9 (52.3)
Dismal	5 (30.1)
Hepatic vein occlusion	4 (23.5)

NOTE: The data are expressed as n (%) or median (IQR); age is presented as median (range).

LIVER TRANSPLANTATION

Out of the 17 patients, 5 (29.4%) who were initially treated received DDLT. Characteristics of patients are presented in Table 4. Further liver-directed therapies

TABLE 2. Characteristics of TARE Treatment (n = 17)

Variable	Value
Body surface area, kg/m ²	1.9 (1.6-2.0)
Lung shunt study, %	4 (2-5)
Treatment target	
Whole	0 (0.0)
Right lobe	2 (11.8)
Left lobe	0 (0.0)
Segmental	7 (41.2)
Multisegmental	8 (47.1)
Targeted liver volume, ml	361 (138-686)
Targeted tumor volume, ml	142 (85-242)
Treatment volume dose, Gy	274 (159-469)
Tumor dose, Gy	400 (217-733)
Whole healthy liver dose, Gy	10 (6-15)
Lung dose, Gy	3.0 (1.9-4.7)
Delivered activity, GBq	1.6 (1.3-2)
Length of hospitalization	
<24 hours	2 (11.8)
24-72 hours	15 (88.2)
>72 hours	0 (0.0)

NOTE: The data are expressed as n (%) or median (IQR).

TABLE 3. Six-Month Response After TARE (n = 14)

Variable	n = 14*
Radiological response of target lesion	
CR/PR	9/5
Radiological response of PVTT	
CR	6 (42.8)
Non-CR/non-PD	6 (42.8)
PD	2 (14.4)
AFP, ng/mL	56 (7.5-434.1)
AFP >100 ng/mL	3 (21.4)
Δ AFP, %	-56 (-91 to +191)

NOTE: The data are expressed as n (%); AFP is presented as median (range) and Δ AFP is presented as median (IQR).

*Three patients died before the evaluation.

were performed before LT in 2 patients who received transarterial chemoembolization (TACE) due to the appearance of a new lesion in the liver at 4 and 22 months after TARE, respectively. Sorafenib was administered in 3/5 patients (60.0%) while patients were on the waiting list. Last imaging (CT or MRI) was performed at a median of 2.1 months (IQR, 1.3-2.8 months) before LT. The median age at the time of LT was 52 years (range, 51-59 years) with a median Model for End-Stage Liver Disease (MELD) score of 12 (IQR, 9-13). LT was

TABLE 4. Characteristics of Patients Submitted to LT (n = 5)

Variable	Value
Age at LT, years	59 (51-59)
MELD-score at LT, points	12 (9-13)
Time between TARE and LT, months	24.9 (6.2-32.6)
Additional locoregional treatments before LT	2 (40.0)
Sorafenib	3 (60.0)
Number of nodules at last imaging	0 (0-1)
Largest nodule at last imaging, mm	0 (0-11)
Last AFP level, ng/mL	4 (2-16)
Recurrence after LT	3 (60.0)
Time between LT and recurrence, months	10.2 (9.7-12.5)
Site of recurrence	
Liver	1
Lung	2

NOTE: The data are expressed as n (%) or median (IQR); age, time between TARE and LT, and time between LT and recurrence are presented as median (range).

performed at a median of 24.9 months after TARE (range, 6.2-32.6 months) and only deceased donor organs were used for this purpose. At explant pathology, only 1 patient had residual liver disease (single nodule, 13 mm, microvascular invasion, G3), whereas another patient had evidence of residual macrovascular invasion.

When the characteristics of the patients submitted to LT after successful downstaging were compared with those who were not transplanted, no significant differences between the 2 groups were found (Table 5). AFP at baseline ($P = 0.10$) and tumor morphology ($P = 0.07$) were close to the limit of significance: there were no AFP producers (AFP > 100 mg/mL)⁽¹⁸⁾ in the transplanted group (versus 41.7%; $P = 0.09$) and 83.3% versus 40.0% of patients had an infiltrative HCC in the nontransplanted group compared with the transplanted group, respectively.

SURVIVAL ANALYSIS

Thirty-day mortality after TARE was 0%. No hospital mortality occurred after LT. At the latest follow-up (December 31, 2020), 14 patients (82.4%) had died and 3 (17.6%; all transplanted) were still alive. The median survival from TARE was 28.3 months (95% CI, 0-58.8). The 1-, 3-, and 5-year OS rates were 70.6%, 58.8% and 14.7%, respectively. Median survival was not reached in the transplanted group compared with 15.1 months (95% CI, 0-39.5) among those who were not transplanted. The 1-, 3-, and 5-year OS rates

TABLE 5. Comparison Between the Transplanted Group and the Nontransplanted Group

Variable	Nontransplanted (n = 12)	Transplanted (n = 5)	P Value
Age, years	54 (48-67)	52 (50-57)	0.38
Sex, male/female	11/1	4/1	0.50
Platelets, n ×10 ³	94 (65-181)	80 (75-156)	
Albumin-bilirubin score			0.95
Grade 1	7 (58.3)	3 (60)	
Grade 2	5 (41.7)	2 (40)	
Number of HCC nodules	1 (1-2)	2 (1-2)	0.33
Maximum diameter, mm	57 (44-69)	67 (31-71)	0.92
Tumor morphology			0.07
Infiltrative	10 (83.3)	2 (40)	
Nodular	2 (16.7)	3 (60)	
AFP, ng/mL	49 (10-555)	7 (5-40)	0.10
AFP > 100 ng/mL	5 (41.7)	0	0.09
PVTT type			0.77
Vp1	2 (16.7)	1 (20)	
Vp2	3 (25)	2 (40)	
Vp3	7 (58.3)	2 (40)	
Milan prognostic score			0.77
Favorable	2 (16.7)	1 (20)	
Intermediate	7 (58.3)	2 (40)	
Dismal	3 (25)	2 (40)	
Hepatic vein occlusion	3 (25)	1 (20)	0.83

NOTE: The data are expressed as n (%) or median (IQR); age is presented as median (range).

were 66.7%, 33.3%, and 0% in the nontransplanted group compared with 80.0%, 80.0%, and 60.0% in the transplanted group, respectively ($P = 0.03$) (Fig. 2A). Such a difference in survival was even greater if all the patients successfully downstaged at 6 months were considered (median survival 54.9 versus 15.1 months, $P = 0.01$).

Median PFS was 12.1 months (95% CI, 5.1-20.1). The 1- and 3-year PFS rates were 58.2% and 12.9%, respectively. Median PFS in the transplanted group was 34.6 months (95% CI, 10.9-58.2) compared with 10.3 months in the nontransplanted group (95% CI, 6.1-14.5; $P = 0.01$). The 1- and 3-year PFS rates were 100.0% and 50.0% in the transplanted group compared with 41.7% and 0% in the nontransplanted group, respectively (Fig. 2B).

Among those who survived up to 6 months but in whom downstaging was unsuccessful, the first site of progression was intrahepatic (n = 4), extrahepatic (n = 3), or

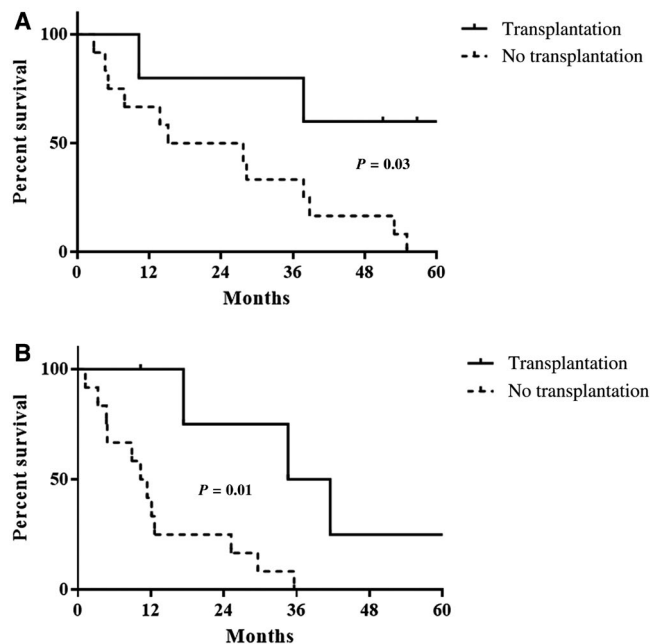


FIG. 2. (A) OS and (B) PFS comparing transplanted with nontransplanted patients.

combined intrahepatic and extrahepatic (n = 2). These patients received either systemic chemotherapy (n = 5) or TACE (n = 4) as palliative treatment according to the underlying liver function and/or extent of disease.

Following LT, 3/5 patients (60.0%) developed recurrence of disease after a median of 10.2 months (range, 9.7-12.5 months). The only patient with hepatic recurrence died 10 months after LT, whereas the remaining 2 patients with pulmonary metastases underwent surgical resection and are currently alive and free from disease. Another patient died in a car accident 5 months after LT, but he had no recurrence at that time. Mammalian targets of rapamycin inhibitors were added to tacrolimus in 2 patients at 13 months (after HCC recurrence) and 10 months (before HCC recurrence) from LT, respectively.

Discussion

This prospective pilot study showed that about 30% of HCC patients with PVTT were successfully downstaged and transplanted after TARE using deceased donors. OS and PFS were both significantly higher among those who received DDLT compared with those who were not transplanted.

Approximately 700,000 deaths occur each year worldwide due to HCC.⁽¹⁹⁾ Despite the widespread of surveillance programs, many patients still present with an advanced disease at the time of diagnosis and their prognosis is unfortunately poor.^(2,3,19) PVTT is present in about 10%-40% of patients^(20,21) and represents a well-recognized negative prognostic factor: the median survival of patients with PVTT ranges between 2 and 4 months and is significantly lower compared with that of patients without it (10-24 months).⁽²²⁾ International guidelines⁽²⁾ recommend sorafenib as the standard treatment for PVTT with survival rates described up to 8 months. However, recent studies have reported longer survival rates in selected patients with partial or complete response (CR) after TARE.^(18,23) In particular, Salem et al.⁽²⁴⁾ showed that 34/291 (12%) patients with advanced HCC were submitted to curative surgery after TARE. In that study, the CR rate was 23% but only 4/92 (4.3%) patients with PVTT underwent LT. Interestingly, the chance of receiving LT was higher among patients with branch PVTT compared with main PVTT. Main PVTT has been found to affect survival negatively in other studies⁽²⁵⁻²⁷⁾; therefore, we decided a priori to exclude these patients from our "Superdownstaging" protocol. Our hypothesis was that selected patients with substantial response to TARE as downstaging therapy could have been potential candidates for DDLT.⁽²⁸⁾

Successful downstaging to within conventional transplantation criteria is a well-recognized favorable prognostic factor in LT.^(12,29,30) Tumor downstaging allows to identify patients who will likely have less recurrences after LT, but more importantly it allows to obtain, in the case of successful downstaging, post-LT results similar to those presenting within criteria,⁽³¹⁾ thus maximizing the concept of transplantation benefit.⁽⁹⁾ Given the dramatic shortage of donors, LDLT rather than DDLT⁽³²⁾ is proposed to treat patients with advanced HCC. Lee et al.⁽³³⁾ described a 5-year OS of 29.8% after LDLT performed in 8 Korean centers for "far advanced" HCC (>10 cm and/or multiples) with or without PVTT. Choi et al.⁽³⁴⁾ reported a slightly better 5-year OS of 42.5% and a recurrence rate of 44.1% in patients with HCC and PVTT without preoperative downstaging. On the contrary, when locoregional treatments such as TACE were applied in the same setting (although radiological response was not taken into account in the decision process), 5-year OS and PFS increased to 63.6% and 45.5%,

respectively.⁽³⁵⁾ In a retrospective study by Jeong et al.,⁽³⁶⁾ TACE was used in combination with radiotherapy to downstage PVTT, with 3-year OS and PFS of 60.5% and 57.8%, respectively. However, no data on the efficacy of downstaging were reported, with LDLT performed at a median of 5 months after TACE (range, 0.4-65.3 months). More recently, downstaging of PVTT has been attempted through stereotactic body radiation with successful downstaging achieved in 63% of cases and LDLT performed in 58% by Soin et al.⁽³⁷⁾ Five-year OS and PFS were better in the downstaged group compared with the nondownstaged group, without reaching statistical significance (57% versus 48% and 51% versus 40%, respectively). Such a small difference, however, might have been related to the short interval between stereotactic body radiation and response evaluation, performed in that study at 4-6 weeks, which could have not allowed for excluding patients with unfavorable disease. In that study, LDLT was performed at a median of 10 weeks after downstaging.

In our study, the effect of TARE on downstaging HCC patients with PVTT was analyzed for the first time in the context of DDLT using an ITT approach. Successful downstaging was achieved in 29.4% of cases and only one-third of the initially enrolled patients were finally submitted to DDLT. According to our previous findings, response to TARE at 3 months was predictive of survival,⁽²⁵⁾ but we established for the current protocol a safer minimum follow-up of 6 months after downstaging to decide whether or not to enlist the patient for LT.⁽²⁴⁾ Nevertheless, although LT was performed at a median of 2 years of CR after TARE (because only deceased donors were used and a sometimes unpredictable waiting time before LT had to be expected) with close imaging evaluations before LT, early recurrence was observed.⁽³⁶⁾ In particular, almost half of the patients experienced extrahepatic recurrence of disease after LT despite a significantly higher PFS in the transplantation group. Hence, it is important to control the disease not only locally but also systemically, before⁽³⁸⁾ and after LT.⁽³⁹⁾ Furthermore, a rare case of isolated cardiac metastasis without venous spreading from the liver⁽⁴⁰⁾ has occurred in a patient enlisted for LT. All these cases should alert physicians when downstaging very advanced HCCs, taking into account that the available imaging techniques may be not accurate enough in evaluating response to treatment.⁽⁴¹⁾

Although the high recurrence rate after LT raises important ethical questions on the use of deceased

donors for patients with HCC and portal vein invasion, it has to be said that most recurrences occurred in the lungs and could be surgically treated. A 5-year OS of 60% after DDLT is one of the longest survivals reported in the literature, considering the potential for 5 years of follow-up and the fact that 1 patient died in a car accident 5 months after LT, thus contributing to decrease the survival rate in the transplanted group. Assalino et al.⁽⁴²⁾ showed a similar OS using deceased donors but only 9/30 transplanted patients were treated with TARE and analyses were not conducted on an ITT basis.

Regardless of downstaging therapy in the study of Assalino et al.,⁽⁴²⁾ only median AFP at the time of LT was significantly different when comparing patients who recurred (>10 mg/mL) with those who did not. In our study, the only patient with an AFP level over 10 ng/mL (19 ng/mL) was the one who died due to progression of disease, confirming in part such a finding. Similarly, Soin et al.⁽³⁷⁾ showed that AFP at baseline (>100 ng/mL) was a poor prognostic factor for OS on multivariate analysis. When we compared pre-operative features between transplanted and nontransplanted patients, AFP at diagnosis was higher in the nontransplanted group without AFP producers in the transplanted group. This aspect underlines the primary role of tumor biology in HCC, and TARE, as every downstaging therapy, should be used to select patients on the basis of biological aggressiveness of disease. Besides, incidence of infiltrative-type morphology was found to be higher in the nontransplanted group, likely indicating the lower probability of response to TARE.⁽⁴³⁾

Our study has some limitations, in particular the small number of patients included which may have rendered the analysis particularly susceptible to bias or prevented significances in baseline characteristics between 2 unbalanced groups. However, the overall sample size conforms well to other previous series of HCC and PVTT. ITT analysis was the main strength of this study, especially considering that it was performed in the setting of DDLT, reinforcing the utility of downstaging in such a context.

In conclusion, TARE was effective in downstaging roughly 30% of patients with HCC and PVTT. Median survival was significantly higher in those patients who could be submitted to LT. However, despite sustained radiological response and subsequent LT, the risk for widespread tumor dissemination via the systemic circulation seemed to be high in these patients. Careful selection for LT must be advised.

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