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Trabalho de Conclusão de Residência

Injeção Percutânea de Etanol para Pacientes com Hepatocarcinoma em Lista para Transplante: Análise de *Dropout* e Desfechos Pós-transplante

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Resumo

Introdução: Terapias locorregionais (LRT) são empregadas para *bridging* e *downstaging* de pacientes com carcinoma hepatocelular (HCC) aguardando transplante de fígado (OLT). Embora as principais opções de terapia locorregionais incluem quimioembolização arterial (TACE), ablação por radiofrequência (RFA), a injeção percutânea de etanol (PEI) é uma opção alternativa com custos consideralvamente menores. Taxas de *dropout* e sobrevida pós-transplante de pacientes submetidos a PEI como LRT ainda não foram meticulsoamente estudados. Este estudo buscou analizar desfechos de PEI como LRT para pacientes com HCC aguardando OLT.

Métodos: Revisão retrospectiva de todos pacientes cirróticos com HCC listados para OLT entre 2011 e 2020 na instituição dos autores. De acordo com a modalidade de LRT, os pacientes foram divididos em 3 grupos: PEI, TACE ou a combinação desses (PEI+TACE). O desfecho primário foi *dropout* de lista devido à progressão tumoral para além dos critérios de Milão. Uma comparação de desfechos pós-transplante estratificada por modalidade de LRT também foi realizada.

Resultados: Cento e sessenta e dois pacientes foram incluídos. Cinquenta e seis receberam PEI, 63 receberam TACE e 43 receberam combinação de PEI e TACE. O *dropout* por prgressão tumoral foi 8.93% no grupo PEI, 14% no grupo PEI+TACE e 14.3% no grupo TACE (p = 0.62). Cento e dezenove pacientes foram ao transplante de fígado. A sobrevida livre de recorrência em 1, 3 e 5 anos foi, respectivamente, 77,7%, 71,7% e 61,1% no grupo PEI, 87,0%, 75,8% e 70,4% no grupo PEI+TACE e 84,4%, 74,9% e 66,9& no grupo TACE. O teste

log-rank não mostrou difereça estatistifcamente significativa em termos de recorrência livre de doença (p=0.55).

Conclusão: PEI é uma terapia-ponte de baixo custo que está associada tanto a taxas de dropout quanto a recorrência livre de doença pós-transplante aceitáveis, desfechos que são comparáveis àqueles obtidos com TACE. Este estudo demonstra evidência que suporta o uso de PEI em pacientes com HCC aguardando OLT em cenários em que RFA não está disponível, especialmente em países com recursos financeiros escassos.

Descritores: injeção percutânea de etanol; hepatocarcinoma; transplante de fígado

Abstract

Background: Locoregional therapy (LRT) is employed for bridging and/or downstaging patients with hepatocellular carcinoma (HCC) awaiting orthotopic liver transplantation. Although the main LRT options include transarterial chemoembolization (TACE) and radiofrequency ablation (RFA), percutaneous ethanol injection (PEI) is an alternative option with considerably lower costs. Dropout rates and post-transplant survival of patients undergoing PEI as LRT have not been thoroughly studied before. This study sought to analyze the outcomes of PEI as LRT for HCC patients awaiting OLT.

Methods: Retrospective review of all cirrhotic patients with HCC listed for OLT between 2011 and 2020 at the authors' institution. According to the LRT modality, the study patients were divided in three groups: PEI, TACE and a combination of those (PEI+TACE). The primary study outcome was waitlist dropout due to tumor progression beyond Milan Criteria. A comparison of post-transplant outcomes of patients as stratified by LRT modality was also included.

Results: One hundred sixty-two patients were included. Fifty-six received PEI, 63 received TACE and 43 received both PEI and TACE. The dropout due to tumor progression rate was 8.93% in the PEI group, 14% in the PEI+TACE group and 14.3% in the TACE group ($p = 0.62$). One hundred nineteen patients underwent OLT. One-, 3- and 5-year post-transplant recurrence-free survival was, respectively, 77.7%, 71.7% and 61.1% in the PEI group, 87.9%, 75.8% and 70.4% in the PEI-TACE group and 84.4%, 74.9% and 66.9% in the TACE group. Log-rank test showed no statistically significant difference in recurrence-free survival ($p = 0.55$).

Conclusions:

PEI is a low-cost LRT bridging therapy that is associated with both acceptable dropout rates and post-transplant recurrence-free survival, outcomes that are comparable to those obtained with TACE. This study provides evidence that supports the use of PEI in HCC patients awaiting OLT in scenarios in which RFA is not available, especially in countries with scarce financial resources.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the seventh most common malignant tumor worldwide and the fourth most common cause of cancer-related death (1). The estimated incidence rate of HCC in cirrhotic patients is 2-4% per year (2). Orthotopic liver transplantation (OLT) represents the ideal treatment option for HCC in the setting of cirrhosis and portal hypertension, since it addresses both the tumor and the underlying chronic liver disease (3-4). The Milan criteria is widely used to identify patients likely to benefit from OLT (5).

Most patients with HCC have a relatively preserved liver function and low calculated MELD scored (6). Thus, most countries worldwide utilize allocation systems that grant exception MELD points to prioritize patients with HCC to OLT. However, many patients still stay long periods in the waitlist, which may lead to tumor progression beyond Milan Criteria and therefore waitlist dropout. For this reason, locoregional therapy (LRT) is recommended if the anticipated waiting time for an organ to become available exceeds 6 months (7). Since the waiting time is often unpredictable, LRT is offered to most patients.

In patients with HCC awaiting OLT, LRT can be used for two purposes: bridging, which aims to prevent tumor progression beyond Milan Criteria; and downstaging, with the goal of reducing tumor mass to meet the Milan Criteria. LRT options include transarterial chemoembolization (TACE), percutaneous ethanol injection (PEI), radiofrequency ablation (RFA) and others. The choice of which LRT is to be used is influenced by tumor size and number, location, liver function and individual center experience (8). In developed countries, RFA is commonly preferred for tumors < 3 cm, whereas TACE or a combination of methods are the treatment options for lesions > 3 cm (9).

Brazil is the third country in number of OLTs performed annually worldwide (10). Since OLT is afforded free of charge to all Brazilian citizens, Brazil has one of the world´s largest liver transplantation systems (11). As RFA is related to an increased cost, unfortunately it is not available for patients treated under the Brazilian public health system (RFA is only afforded to Brazilian patients who have private insurance). Thus, in Brazil most cirrhotic patients with HCC undergo only PEI, TACE or a combination of both methods as bridging and/or downstaging therapies to HCC while in the OLT waitlist. The aim of this study was to analyze the outcomes of PEI as LRT for HCC patients awaiting OLT. Specifically, liver transplant list dropout rate due to tumor progression, post-transplant overall and recurrence-free survivals all were evaluated here.

Patients and Methods

All cirrhotic patients with HCC listed for OLT between 2011 and 2020 at the authors' institution were studied. Patients whose HCC was within Milan Criteria were included. Patients whose HCC was beyond Milan Criteria also were included in this analysis. As only a very small number of patients underwent RFA as LRT (six), these patients were not included in this study.

For each nodule, the choice of LRT modality (TACE, PEI or both methods) was accomplished by a consensus of liver transplant surgeons, hepatologists and interventional radiologists. Follow-up images (contrast-enhanced computed tomography [CT] or magnetic resonance imaging [MRI]) were obtained 6-8 weeks after the procedure and the need for subsequent therapies was decided based on the presence of viable residual tumor on CT or MRI.

PEI was performed by one of the two experienced interventional radiologists through CT or ultrasound guidance. Puncture was performed using a 20-gauge needle under sedation.

TACE was performed by one of two experienced interventional radiologists through femoral access under sedation. A Cobra of Mikaelson 5 F catheter was used to achieve selective catheterization and arteriogram of celiac trunk and superior mesenteric artery. The tumor feeding artery was selectively catheterized using a 2.8 F microcatheter (Progreat, Terumo ®). Doxorubicin-Lipiodol Emulsion followed by Polyvinyl alcohol (PVA) or microspheres with particles sized 100–300 micrometers were infused. Until the year of 2012, bland transarterial embolization (TAE) was the only modality of embolization available at the Brazilian public health system (12). The present study includes patients treated from 2011 to 2020. Since only a small number of patients in this cohort underwent TAE, all transarterial procedures were classified as TACE.

Contrast-enhanced CT or MRI was used to characterize preprocedural disease extent, including size and number. Number of lesions encompasses only tumors classified as LIRADS 4 and 5 on radiological report. MELD score was calculated according to Malinchoc et al (13). Preprocedural alpha-feto-protein (AFP) was defined as the AFP immediately before the first LRT.

Patients enlisted for OLT underwent PEI, TACE or a combination of both (PEI+TACE). HCC patients listed for OLT who did not undergo any LRT were excluded from this study. Patient demographic variables included age, gender, etiology of cirrhosis, calculated MELD score, preprocedural AFP, number of lesions, diameter of the largest tumor and number of procedures.

According to the LRT modality, the study patients were divided in three groups: A) PEI, B) TACE and C) PEI+TACE. The primary study outcome was waitlist dropout due to tumor progression beyond Milan Criteria. Secondary outcomes were 1) Pathological response (as assessed by dedicated liver pathologists who also evaluated the tumor for vascular invasion); 2) Side effects of LRT (as graded by the Clavien-Dindo classification) (14); 3) Post-transplant HCC recurrence, as evaluated by post-transplant recurrence-free survival. Patients were followed up until their death, waitlist dropout or end of the study on 30th June, 2021. As the primary outcome was evaluated using the Kaplan-Meier method, patients who underwent OLT were censored on the transplant date.

Time to dropout due to tumor progression was defined as the number of days between first LRT and dropout date. Time to recurrence or death was defined as the number of days between OLT and either of those events. Pathological response and tumor vascular invasion were assessed by dedicated liver pathologists. Complete or near complete pathological response was defined as tumor necrosis equal to or greater than 90% on pathological report of the explanted liver of patients who underwent OLT. A comparison of the post-transplant outcomes of patients as stratified by LRT modality also was included.

Categorical variables were compared using Chi-square test. Normality test of continuous variables was estimated through the Kolmogorov–Smirnov method. Continuous variables were analyzed with Kruskal-Wallis test or ANOVA as appropriate. Univariate analysis was performed through the Cox proportional hazards regression method. For both primary and secondary endpoints, variables with a p-value < 0.1 in the univariate analysis were pulled into multivariate Cox proportional hazards regression analysis to identify independent risk factors

associated with the two study endpoints. Waitlist dropout was analyzed using Kaplan–Meier method, and survival comparisons among subgroups were performed using log-rank test. Post-transplant survival and HCC recurrence were also both evaluated using Kaplan–Meier method. Except for the univariate analysis, a p-value < 0.05 was considered as statistically significant. Analysis was performed using R version 4.0.3 (15).

Results

Over the 10-year study period, 184 patients with HCC were enlisted for OLT. Six patients who underwent RFA, 8 patients who did not undergo any LRT and 8 additional patients whose diagnosis of HCC was made incidentally in the explanted liver were excluded, resulting in a total of 162 patients included in this study. Of these, 56 received PEI, 63 received TACE and 43 received both PEI and TACE.

Recipient, tumor and treatment characteristics are shown in table 1. Overall, the median age was 59 (IQR: 55 - 69), and 101 (62%) patients were male. The most common etiology of cirrhosis was HCV infection, which was present in 128 (79%) patients. The median calculated MELD score was 10 (IQR: 8 - 12), and median pre-procedure AFP was 13 (IQR: 5.2 - 57). Ninety-eight patients (60.5%) had only one lesion, 42 (25.9%) had 2 lesions, 19 (11.7%) had 3 lesions and only 3 (1.9%) patients had 4 or more lesions. Twenty-two (13.6%) patients were outside the Milan criteria on preprocedural imaging. All those patients were downstaged (4 PEI, 7 TACE, 11 PEI+TACE). The median largest tumor diameter was 2.7 cm (IQR: 2.2 - 3.3). The median number of procedures was 2 (IQR: 1 - 3).

A comparison of baseline characteristics between the three groups showed statistically significant differences in mean preprocedural AFP (PEI 6.1 ng/ml *vs.* TACE 38.3 ng/ml *vs.* PEI+TACE 15.2 ng/ml) (p = 0.002), median largest tumor diameter (PEI 2.2 cm *vs.* TACE 3 cm *vs.* PEI+TACE 2.9 cm) (p < 0.001), percentage of patients outside Milan criteria (PEI 7.1% *vs.* TACE 11.1% *vs.* PEI+TACE 25.6%) and median number of procedures (PEI 1 *vs.* TACE 1 *vs.* PEI+TACE 3) (p < 0.001). Other patients' characteristics were comparable between the groups.

Dropout Due to Tumor Progression

The dropout due to tumor progression rate was 8.93% in the PEI group *vs.* 14.3% in the TACE group *vs*. 14% in the PEI+TACE group (p = 0.62) (Table 2). The Kaplan-Meier analysis for dropout due to tumor progression is shown in Figure 1. The hazard ratio for TACE *vs*. PEI was 1.98 (CI 95% = 0.65 – 6) and 1.41 (CI 95% = 0.43 - 4.7) for PEI+TACE *vs.* PEI (p-value for comparison among the 3 groups = 0.46).

Univariate analysis using Cox proportional hazards regression was performed to identify variables associated with increased dropout due to tumor progression rate (Table 3). Preprocedural AFP greater than 10 was associated with increased likelihood of dropout due to tumor progression (HR = 4.8, 95% CI = 1.4 - 17, p = 0.003). As this was the only variable associated with statistically significant differences, multivariate analysis was not performed.

Pathological Response

Complete or near-complete pathological response was achieved by 7 (17.1%) patients in the PEI group, 9 (20%) of patients in the TACE group and 7 (21.2%) patients in the PEI+TACE group. The difference was not statistically significant (p = 0.89).

Downstaging

Of the 162 patients, 22 (13.5%) had tumor burden beyond Milan criteria before the first procedure and underwent LRT with the intent of downstaging. Baseline and treatment characteristics are shown in Table 4. Four of these patients were downstaged through PEI only, 7 through TACE only and 11 through both PEI and TACE. For these 22 patients who were downstaged, the dropout rate was similar among LRT methods [1/4 (25%) in the PEI group *vs*. 2/7 in the TACE group (28.6%)] *vs*. 2/11 (18.2%) in the PEI+TACE group (p = 0.87)].

The dropout due to tumor progression rate was 22.7% (5/22) in Milan-out patients *vs.* 10.7% (15/140) in Milan-in patients (p = 0.21). Fourteen patients underwent OLT after successful downstaging. The recurrence-free survival of these patients was similar to that of bridging patients (Figure 2).

Adverse Events

Of the 56 patients who underwent PEI, 3 (5.4%) experienced adverse events, all of which were classified as Clavien-Dindo 2 or lower. In the TACE group (n = 63), there were 6 (9.5%) adverse events, all of which were Clavien-Dindo 2 or lower. There were four (9.3%) adverse events in the PEI+TACE group (n = 43). One of the 4 patients who had adverse events in the PEI-TACE group died due to hemorrhage following a combined procedure of PEI and TACE. The other 3

adverse events in the PEI+TACE group were classified as Clavien-Dindo 1. Altogether, there was no statistically significant difference in adverse event rate between the groups (p = 0.66) (Table 5).

Post-Transplant Outcomes

Of the 162 patients included in the study, 119 underwent OLT. Demographic and treatment characteristics are shown in Table 6. Overall, the median age was 59 (IQR: 55 - 63.5), and 76 (63.9%) were male. The most common etiology of cirrhosis was HCV infection, which was present in 92 (77%) patients. The median calculated MELD score was 10 (IQR: 8.5 - 12) and the median pre-transplant AFP was 10.25 (IQR: 8.5 - 12). Seventy-four patients (62.2%) had only one lesion, 27 (22.7%) had 2 lesions, 15 (12.6%) had 3 lesions and 3 (2.5%) had 4 or more lesions. The median largest tumor diameter was 2.6 cm (IQR: 2.2 - 3.3), and there were 14 patients outside the Milan criteria on preprocedural imaging (11.8%). Complete or near-complete pathological response was achieved in 23 (19.3%) and vascular invasion was detected in 23 (19.3%) patients. As stated in the pathological response, there was no difference in the complete or near-complete pathological response rate among the three groups.

A comparison of baseline characteristics between the three groups showed a small but statistically significant difference in the median largest tumor diameter (2.2 cm for PEI *vs*. 3 cm for TACE *vs*. 2.7 cm PEI+TACE) (p < 0.001). There were no statistically significant differences between PEI, TACE and PEI+TACE in the other comparisons, including complete or near complete pathological response and vascular invasion.

Post-Transplant Recurrence-Free Survival and Overall Survival

At the time of analysis, median post-transplant follow-up time was 47 months. The overall survival at 1, 3 and 5 years was, respectively, 77.7%, 71.7% and 61.1% in the PEI group, 84.4%, 74.9% and 66.9% in the TACE group (p = 0.46) and 87.9%, 75.8% and 70.4% in the PEI+TACE group. In terms of overall survival, The hazard ratio for TACE *vs*. PEI was 0.84 (CI 95% 0.43 – 1.6) and 0.59 (CI 95% 0.24 – 1.4) for PEI+TACE *vs*. PEI (Figure 3a).

The recurrence-free survival at 1, 3 and 5 years was, respectively, 77.7%, 62.9% and 55.6% in the PEI group, 84.4%, 65.7% and 60.8% in the TACE group and 78.2%, 70.4% and 65.5% in the PEI+TACE group (p = 0.55). The hazard ratio for TACE vs. PEI was 0.91 (CI 95% 0.49 – 1.71) and 0.66 (CI 95% 0.3 – 1.4) for PEI+TACE vs. PEI (Figure 3b).

Univariate analysis using Cox proportional hazards regression was performed to identify variables associated with decreased recurrence-free survival rate (Table 7). Vascular invasion was associated with decreased likelihood of recurrence-free survival (HR 2.7, 95% CI 1.5 - 4.8, p= 0.002). Complete/near complete pathological response showed a trend towards improving recurrence-free survival (HR 0.47, 95% CI 0.2 - 1.1, p = 0.058), but the results did not reach significance. However, since p-value was less than 0.1 for these two variables, both were pulled into multivariate analysis. Results are shown in Table 8. Vascular invasion remained associated with decreased likelihood of recurrence-free survival (HR 2.71, 95% CI 1.49 - 4.9, p = 0.001). Complete/near complete pathological response was also not associated with a statistically significant difference in recurrence-free survival.

Discussion

OLT provides excellent outcomes to patients with HCC within Milan Criteria (5). However, due to organ shortage and consequently long periods in the waitlist, many tumors progress beyond Milan Criteria, resulting in waitlist dropout. Although the role of LRT in patients awaiting OLT remains uncertain, international guidelines recommend the use of LRT as bridging to transplant (4, 16, 17), despite the absence of randomized controlled trials (RCTs) to support it. This decision is based on studies evidencing a 1- and 2-year dropout rate as high 25% and 43%, respectively, in patients who do not undergo any LRT (18, 19). Additionally, evidence from retrospective studies support LRT as an effective way of both decreasing dropout rate and improving post-transplant outcomes (8, 20, 21).

The choice of which pretransplant LRT strategy to be employed remains to be elucidated. As definitive treatment to patient with a single small HCC not candidates for OLT, RCTs show that RFA is associated with improved overall survival (22), recurrence-free survival (23) and sustained complete response (24) as compared to PEI. In developed countries, RFA, TACE or a combination of both methods are the most employed strategies for bridging HCC to OLT. However, definitive evidence of superiority of RFA over PEI and TACE as a bridging therapy to OLT is still lacking. There is only one previous study comparing different LRTs strategies with regards to dropout rates. In that observational study, the use of RFA as a single LRT method was associated both with lower tumor progression and decreased dropout rates as compared to TACE only and PEI/PAI (percutanous acetic acid injection) only (25). Of note, most patients in that study had HBV infection (53%), which at least in part would limit the extrapolation of

the results to Western populations. Pompilli et al (9) evaluated a total of 46 nodules which were bridged to OLT. The authors detected a higher rate of complete pathological necrosis in the liver explant of patients who received RFA compared to patients who received PEI as bridging. However, dropout rate and tumor progression rate were not evaluated in that study.

To the best of our knowledge, there is no prior study evaluating dropout rates of patients bridged with PEI as compared to TACE. This is the first study evaluating PEI, TACE and with a combination of these modalities in terms of dropout and posttransplant outcomes. The current study reports on the natural history of patients with HCC bridged to OLT with PEI. We evaluated a total of 162 patients with HCC enlisted for OLT undergoing LRT as either bridging or downstaging in a single center in Brazil. Since RFA is not available in the Brazilian Public Health System, all patients underwent PEI, TACE or a combination of both methods. The majority of patients (86%) in the present study had HCC within Milan Criteria. There was no statistically significant difference in the dropout rate due to tumor progression among the three groups (PEI, TACE and PEI+TACE). Castroagudin et al (26) performed a single-arm observational study evaluating PEI as LRT prior to OLT. A total of 27 patients underwent bridging with PEI of which 19 were transplanted. The authors detected a dropout out rate due to tumor progression of 7.4 % (2/27). Another study by Branco et al (27) evaluated a total of 62 OLT candidates treated with PEI vs. 35 who did not receive any LRT. Three dropouts were reported in each of the two groups, accounting for 4.8% in the PEI group and 8.5% in the control group. The difference was not statistically significant, likely because of small study sample.

Of the 162 patients enlisted for OLT in the present study, 119 underwent OLT. Post-transplant recurrence-free survival and overall survival did not differ significantly among the three treatment groups (PEI vs. TACE vs. PEI+TACE). Also, the complete/near complete pathological response was comparable across all the treatment groups. The complete/near-complete dropout rate of our study is lower than that of the few prior studies that evaluated PEI as bridging (26, 27). We ascribe that discrepancy to the fact that we were unable to perform a per tumor analysis. Therefore, we performed a per patient analysis, and complete/near complete pathological response was analyzed taking the whole specimen into consideration. Specifically, several patients had a complete necrosis of a main large tumor, but had small viable HCCs that had not been on the pre-transplant imaging.

One of the most striking results of this study was the effectiveness of PEI or PEI+TACE to downstage patients with HCC outside the Milan criteria. While TACE and RFA results are frequently reported in the literature (28, 29, 30), there are only very few studies reporting on PEI as a potential option for downstaging (31, 32). In this study, PEI only or a combination of PEI+TACE were used to downstage 15 patients, 10 of which underwent OLT. Four additional patients were transplanted after successful downstaging with TACE only. Altogether, these patients' post-transplant HCC recurrence-free survival was comparable to that of patients whose HCC was within Milan criteria.

Another issue that deserves attention is the one of cost-effectiveness. In Brazil, the estimated cost associated with PEI is under U$ 200 for each therapy session. Each TACE procedure in our hospital has an average cost of U$ 2000. Notably, the cost of each RFA session is nearly U$ 3000. In contrast to RFA, PEI

and TACE are both covered by the Brazilian Public Health System, thus being cost-free to every Brazilian citizen. In the RCT performed by Brunello et al (24), in patients with small HCCs, the extra cost per one additional patient achieving a sustained CR at 1 year, by using the RFA instead of PEI, was 8,286 euros.

In univariate Cox regression analysis, the only variable that was significantly associated with an increase in the dropout rate was pre-procedure AFP. This is in consonance with results of the recent study performed by Mehta et al (33). In that study, increased MELD-Na score, higher number of tumors and tumor size > 3 cm also were associated with increased dropout rate. Regarding post-transplant outcomes, the present study found that vascular invasion was the only statistically significant predictor of HCC recurrence-free survival. Similarly, Seehofer et al (21) also found an association between vascular invasion and HCC recurrence. In a study by Agopian et al (34), who analyzed the outcomes of 501 patients undergoing OLT following LRT, complete pathological response was the strongest predictor of post-transplant overall survival. Other predictors were pretransplant AFP and radiologic maximum diameter. In our study, complete/near complete pathological response showed a trend towards significance in both uni and multivariate Cox regression analysis. The possibility of a type II error cannot be excluded. In other words, the lack of significance could be related to the relatively small sample size of our study (n = 119).

Our study has some limitations. The first one, is its retrospective and single-center study, potentially prone to local biases. However, all of the decisions for HCC treatment were made by a multidisciplinary team composed by liver transplant hepatologists, surgeons and interventional radiologists that are familiar with PEI, TACE and RFA. Also, most of the medical and surgical team remained

unchanged during the period in this center in the majority of the transplants included in this cohort. This may strengthen the homogeneity of the population and the selection criteria, increasing the internal validity of this study. Another potential limitation is that most patients in this cohort had HCV (79%). Therefore, results should be interpreted with caution for populations in which HCV do not predominate. Conversely, since HCV is still the leading cause of LT in most western countries, including the USA (35, 36), examining the outcomes of patients undergoing LT for HCV remains hugely relevant.

In conclusion, the use of PEI as bridging and/or downstaging therapy for HCC patients awaiting OLT is associated with acceptable dropout rates. Furthermore, bridging to OLT with PEI was associated with post-transplant overall and recurrence-free survivals that are comparable to those of TACE bridging. The association of PEI with TACE also led to acceptable outcomes. Thus, considering the relative low-cost of PEI, this study provides evidence favoring the use of PEI (alone or in combination with TACE) patients with HCC awaiting OLT in situations in which RFA is not an option, such as tumors in the vicinity vascular structures. Additionally, routine use of PEI for bridging to OLT also may be justified whenever RFA is unavailable, such as in several developing countries.

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TABLES

Table 1: Baseline characteristics of the cohort according to treatment group.

	Overall	PEI	TACE	PEI+TACE	*p-value*
n	162	56	63	43	
Age (years), median [IQR]	59 [55, 64]	58 [55, 62]	60 [55, 64]	60 [56.5, 65]	0.368
Male sex, n (%)	101 (62.3)	37 (66.1)	33 (52.4)	31 (72.1)	0.094
Diagnosis, n (%)					0.774
HCV	128 (79.0)	43 (76.8)	48 (76.2)	37 (86.0)	
HBV	9 (5.6)	2 (3.6)	5 (7.9)	2 (4.7)	
Alcohol	14 (8.6)	7 (12.5)	5 (7.9)	2 (4.7)	
NASH	7 (4.3)	2 (3.6)	3 (4.8)	2 (4.7)	
Other	4 (2.5)	2 (3.6)	2 (3.2)	0 (0.0)	
Calculated MELD score, median [IQR]	10 [8, 12]	11 [8, 14]	10 [8, 11]	11 [9, 13]	0.081
Preprocedural AFP, median IQR]	13 [5.2, 57]	6.1 [4.7, 21.2]	38.3 [6.9, 101.2]	15.2 [5.4, 33.4]	**0.002**
Number of lesions, n (%)					0.082
1	98 (60.5)	37 (66.1)	43 (68.3)	18 (41.9)	
2	42 (25.9)	13 (23.2)	13 (20.6)	16 (37.2)	
3	19 (11.7)	4 (7.1)	7 (11.1)	8 (18.6)	
≥4	3 (1.9)	2 (3.6)	0	1 (2.3)	
Largest tumor diameter, median [IQR]	2.7 [2.2, 3.3]	2.2 [2.0, 2.6]	3 [2.6, 3.9]	2.9 [2.3, 3.7]	**<0.001**
Milan-out, n (%)	22 (13.6)	4 (7.1)	7 (11.1)	11 (25.6)	**0.023**

Number of procedures, median [IQR]	2 [1, 2]	1 [1, 2]	1 [1, 2]	3 [2, 3]	**<0.001**

Table 2: Comparison of dropout due to tumor progression according to treatment group

	Dropout due to tumor progression		
	No	Yes	*p-value*
	n (%)	n (%)	
PEI	51 (91.1)	5 (8.9)	0.62
TACE	54 (85.7)	9 (14.3)	
PEI+TACE	37 (86)	6 (14)	

Table 3: Univariate analysis for dropout due to tumor progression rate using Cox proportional hazards regression

	Cox Regression		
	HR	[IC95%]	*p-value*
Age > 60	0.89	[0.37 - 2.2]	0.8
Male sex	0.72	[0.3 - 1.7]	0.45
HCV diagnosis	1.5	[0.43 - 5]	0.51
Size < 3 cm	0.6	[0.24 - 1.5]	0.28
Single nodule	0.63	[0.26 - 1.5]	0.3
Preprocedural AFP > 10	4.8	[1.4 - 17]	**0.003**
Milan-out	1.7	[0.61 - 4.7]	0.308

Table 4: Baseline characteristics of downstaged patients

	PEI	TACE	PEI+TACE	*p-value*
n	4	7	11	
Age (years), median [IQR]	55 [54.7, 58.0]	57[56, 62]	60 [58, 62]	0.450
Male sex, n (%)	4 (100)	4 (57.1)	5 (45.5)	0.163
Diagnosis, n (%)				NaN
HCV	3 (75)	4 (57.1)	10 (90.9)	
HBV	0 (0)	1 (14.3)	0 (0)	
Alcohol	1 (25.0)	1 (14.3)	1 (9.1)	
NASH	0 (0)	0 (0)	0 (0)	
Other	0 (0)	1 (14.3)	0 (0)	
Calculated MELD score, median [IQR]	10.5 [9.2, 14.7]	10 [9, 11.5]	11 [8.5, 13]	0.846
Preprocedural AFP, median IQR]	2.9 [2.6, 5]	25.9 [5.1, 67.4]	15.5 [10.7, 21.5]	0.206
Number of lesions, n (%)				0.246
1	0 (0)	3 (42.9)	2 (18.2)	
2	1 (25)	3 (42.9)	5 (45.5)	
3	1 (25)	1 (14.3)	3 (27.3)	
≥4	2 (50)	0 (0)	1 (9.1)	
Largest tumor diameter, median [IQR]	3 [2.4, 3.4]	5 [3.5, 5.4]	4 [3.6, 5.1]	0.078
Number of procedures, median [IQR]	1.5 [1, 2]	2 [1, 2]	3 [3, 3.5]	**0.001**

Table 5: Adverse events according to treatment group

	Adverse events		
	No	Yes	*p-value*
	n (%)	n (%)	
PEI	53 (94.6)	3 (5.3)	0.66
TACE	57(90.5)	6 (9.5)	
PEI+TACE	39 (90.7)	4 (9.3)	

Table 6: Baseline characteristics of patients who underwent OLT

	Overall	PEI	TACE	PEI+TACE	p
n	119	41	45	33	
Age (years), median [IQR]	59 [55, 63.5]	58 [55, 61]	6 [54, 65]	60 [56, 64]	0.247
Male sex, n (%)	76 (63.9)	28 (68.3)	25 (55.6)	23 (69.7)	0.336
Diagnosis, n (%)					0.474
HCV	92 (77.3)	29 (70.7)	35 (77.8)	28 (84.8)	
HBV	8 (6.7)	2 (4.9)	4 (8.9)	2 (6.1)	
Alcohol	11 (9.2)	6 (14.6)	4 (8.9)	1 (3.0)	
NASH	6 (5.0)	2 (4.9)	2 (4.4)	2 (6.1)	
Other	2 (1.7)	2 (4.9)	0 (0)	0 (0)	
Calculated MELD score, median [IQR]	10 [8.5, 12]	11 [9, 13]	9 [8, 11]	11 [9, 12]	0.118
Pre-transplant AFP, median [IQR]	10.2 [4.5, 41.1]	6.9 [4.4, 22.8]	11.1 [4.5, 51.4]	12.3 [5, 42.5]	0.425
Number of lesions, n (%)					0.396
1	74 (62.2)	27 (65.9)	31 (68.9)	16 (48.5)	
2	27 (22.7)	8 (19.5)	8 (17.8)	11 (33.3)	
3	15 (12.6)	4 (9.8)	6 (13.3)	5 (15.2)	
≥4	3 (2.5)	2 (4.9)	0 (0)	1 (3.0)	
Largest tumor diameter, median [IQR]	2.6 [2.2, 3.3]	2.2 [2, 2.6]	3.0 [2.5, 3.6]	2.7 [2.3, 3.7]	<0.001
Milan-out, n (%)	14 (11.8)	3 (7.3)	4 (8.9)	7 (21.2)	0.137
Complete or near complete pathological response (%)	23 (19.3)	7 (17.1)	9 (20)	7 (21.2)	0.895
Vascular invasion (%)	23 (19.3)	11 (26.8)	6 (13.3)	6 (18.2)	0.280

Table 7: Univariate analysis for recurrence free survival after OLT using Cox proportional hazards regression

	Cox Regression		
	HR	[IC95%]	*p* value
Age	0.65	[0.37 -1.1]	0.13
Sex	1	[0.56 - 1.8]	0.98
HCV diagnosis	0.65	[0.35 - 1.2]	0.2
Size < 3 cm	1.1	[0.62 - 2.1]	0.66
Single nodule	1.1	[0.6 - 1.9]	0.79
Milan-out	1.2	[0.54 - 2.7]	0.66
Pre-transplant AFP	0.77	[0.4 - 1.5]	0.43
Complete/near complete pathological response	0.47	[0.2 - 1.1]	0.058
Vascular invasion	2.7	01.5 - 4.8]	0.002

Table 8: Multivariate analysis for recurrence free survival after OLT using Cox proportional hazards regression

	Cox Regression		
	HR	[IC95%]	*p*
Complete/near complete pathological response	0.45 (0.19 - 1.1)	[0.19, 1.1]	0.07
Vascular invasion	2.71	[1.49, 4.9]	0.001

FIGURES

Figure 1: Kaplan-Meier analysis for dropout due to tumor progression

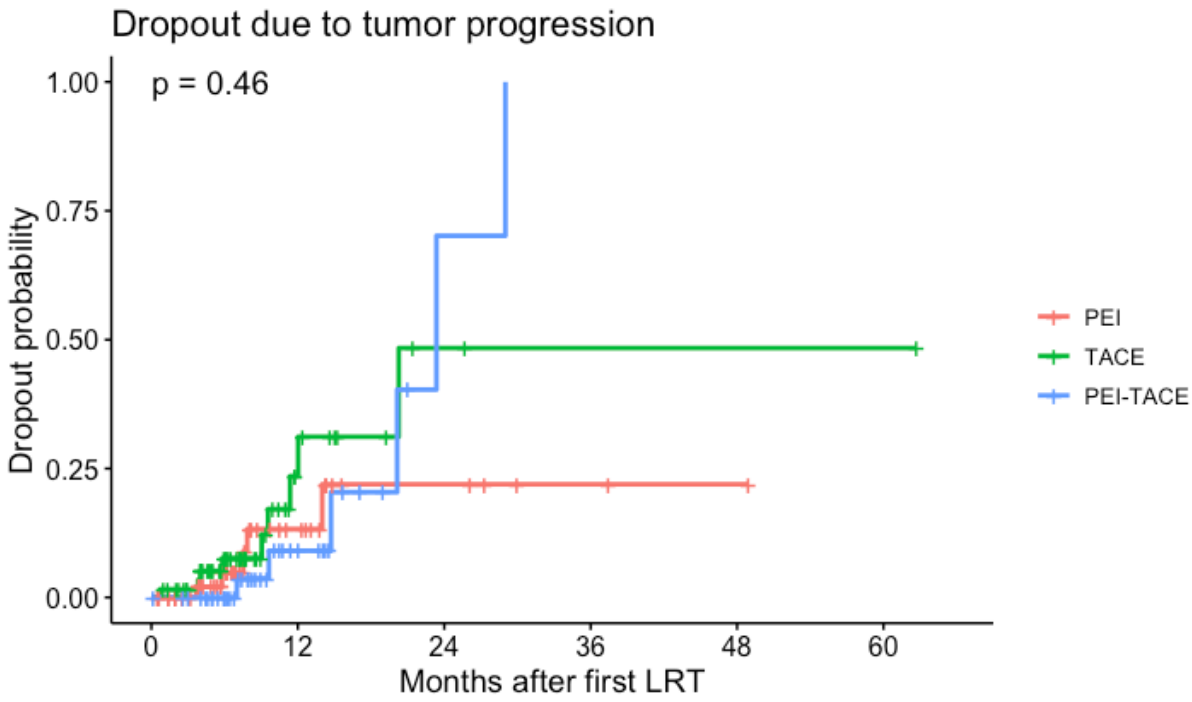

Figure 2: Recurrence-free survival after OLT for bridging vs.downstaging

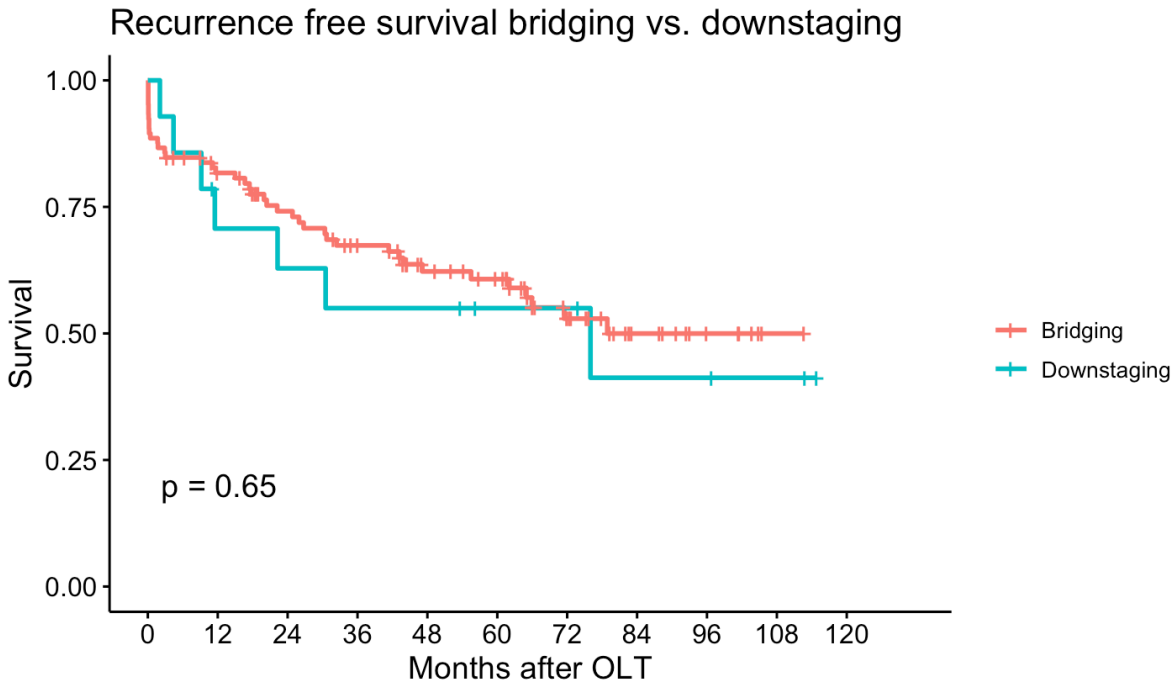

Figure 3a: Overall survival after OLT

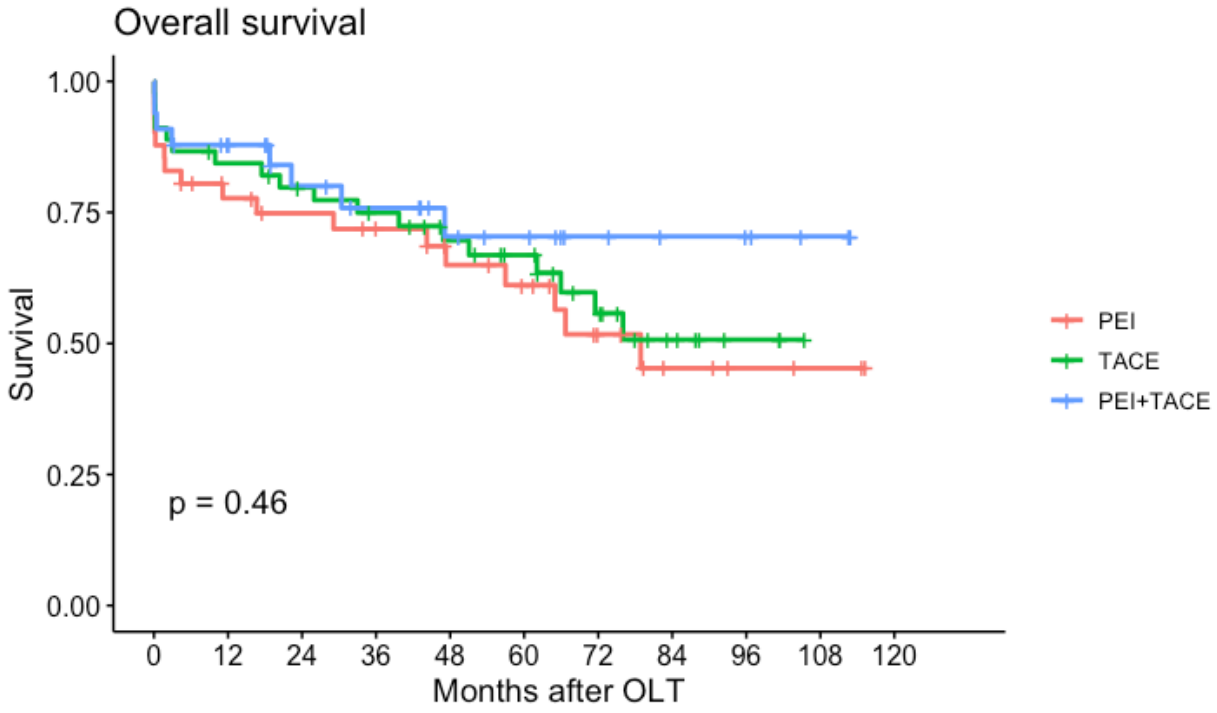

Figure 3b: Recurrence-free survival after OLT