Liver Transplantation in Patients With Hepatocellular Carcinoma Outside the Milan Criteria After Downstaging: Is It Worth It?

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ABSTRACT

Background. The outcome of orthotopic liver transplantation (OLT) for hepatocellular carcinoma (HCC) is excellent if it is performed within the Milan criteria (ie, single tumor less than 5 cm or 3 tumors less than 3 cm each one and no macrovascular invasion). However, after a few studies, it has become possible to have a similar survival expanding those criteria. The aim of this study is to evaluate the survival of patients with advanced HCC who, after downstaging, did not met the Milan criteria although they were within the "up to seven" benchmark, and were transplanted at our center in the last 5 years.

Patients and Methods. This is a retrospective study of patients who underwent OLT for HCC in the last 5 years in our center exceeding Milan criteria despite remaining within the "up to seven" benchmark. An observational study of associated factors with overall survival based on patient characteristics after OLT was performed. For the statistical study, the statistical program SPSS v. 17.0 (Chicago, Illinois, United States) was used.

Results. We studied 95 patients who had been transplanted for HCC in this period, 11 of whom met the study requirements. There were 10 (91%) males and 1 female. The mean age of the patients was 54.73 ± 8.75 years, with an average waiting list time of 279 days. Nine patients had a Child A status, with a mean Model for End-stage Liver Disease score of 9.64 (range, 6 to 16). The most frequent etiology of cirrhosis was hepatitis C virus infection in 6 patients (50%) followed by hepatitis B virus infection and ethanolic and cryptogenic cirrhosis. Ten patients (91%) had at least one pretransplantation transarterial chemoembolization. The survival of patients after 1 year was 75%, whereas after 4 years that rate decreases to 25%. At this time, we do not have any patients with a 5-year survival rate. The longest survival rate is 55 months.

Conclusions. Although the expanded indication of transplantation in HCC raises controversies, especially after downstaging, it is possible to provide acceptable survival rates for patients within the expanded criteria of "up to seven" after locoregional therapies. The performance of a liver transplant in the patient profile shown in this article should also be evaluated from the perspective of the relative lack of organs for transplantation.

HEPATOCELLULAR CARCINOMA (HCC) is an aggressive tumor entity, with the only curative options being surgical resection or orthotopic liver transplantation (OLT). However, the percentage of patients in which resection or OLT are possible is usually below 20%, mainly

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Table 1. Patient Characteristics

No.	Gender	Age (Years) (Mean 54.73 ± 8.75)	Waiting List (Days) (Mean 279.73 ± 163.69)	Child	Meld (Mean 9.54 ± 2.80)	HCV	Locoregional Therapy	Postoperative Death	Liver Retransplantation	Graft Survival (Days)	Overall Survival (Days)	Overall Survival (Months)	Death
1	M	35	268	A	10	NO	TACE	NO	NO	1126	1126	37	YES
2	M	62	171	A	8	NO	TACE	NO	NO	1645	1645	55	NO
3	M	55	222	A	9	NO	TACE	NO	NO	1423	1423	48	NO
4	M	55	288	A	6	YES	TACE	YES	NO	67	67	2	YES
5	M	56	225	B	16	YES	RFR+OH	YES	NO	37	37	1	YES
6	M	52	210	A	7	YES	TACE	YES	NO	114	114	3	YES
7	F	50	353	B	10	NO	TACE	NO	NO	1062	1062	35	NO
8	M	58	110	A	11	YES	TACE	NO	NO	334	334	11	NO
9	M	64	682	A	12	NO	TACE	NO	NO	319	319	11	NO
10	M	67	118	A	7	YES	TACE	NO	NO	283	283	10	NO
11	M	48	430	A	10	YES	RFR+TACE	NO	NO	247	247	8	NO

because the diagnosis of the tumor is usually late; therefore, patients are in an advanced disease stage. Furthermore, resection is often not possible because of the degree of the underlying liver disease and the risk of deterioration of the liver function post-resection [1]. Another obstacle for patients with HCC is the shortage of organs for OLT, which has led to the introduction of strict and restrictive selection criteria. These criteria are exclusively based on morphological parameters (size and number of nodules), with contrast computed tomography and magnetic resonance imaging being the main tools used for the diagnosis and stratification of HCC [2,3]. The Milan criteria (MC) constitute the clinical situation in which the best results for OLT in patients with HCC have been achieved [4]. Factors such as alpha fetoprotein levels, the degree of tumor differentiation, and vascular invasion have also been clearly correlated with post-OLT results in patients with HCC [5]. However, these also have their limitations.

Patients initially beyond the MC may be subjected to downstaging to reduce tumor size to meet the MC. Locoregional therapies are used, including transarterial chemoembolization (TACE), radiofrequency ablation, transarterial radioembolization, and percutaneous ethanol injection [6]. Better survival rates may occur in these patients with good responses to downstaging therapy followed by waiting at least 3 months after locoregional therapy to re-evaluate the liver transplantation decision for patients with HCC beyond the MC [7]. With careful criteria for patient selection and the use of locoregional therapy before OLT, good results can be obtained for patients beyond the MC who had no better chance than OLT [8]. In this study, we reviewed 11 of 95 patients with HCC undergoing OLT who were beyond the MC but within the "up to seven" benchmark. Based on this HCC patient cohort, the present study aimed to evaluate the survival rates between different tumor stages and determine the impact of locoregional therapies.

PATIENTS AND METHODS

Up to December 31, 2016, we registered a total of 1257 OLT patients (Table 1). The subject selection process is based on the Barcelona Clinic Liver Cancer scheme for patients with HCC. After analyzing the Child–Model for End-stage Liver Disease score and tumor stage, we included the selected patients on the waiting list, after which they underwent treatment with locoregional therapies by receiving imaging studies to assess whether downstaging their criteria or dropping out would be worse. Patients were excluded for OLT if there was extrahepatic metastasis and if vascular invasion were detected before OLT. Endpoints for the current analysis were overall and graft survival rates and tumor recurrence during follow-up. Overall, graft and tumor-free survival rates were calculated using the Kaplan–Meier method from the date of OLT.

RESULTS

Ninety-five patients were transplanted for HCC during the study period. Eleven (12%) of them met the study requirements (10 males and 1 female). The mean age of the patients was 54.73 ± 8.75 years, with an average waiting list