ORIGINAL ARTICLE

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Indicators of Recurrence Before and After Transplantation in Patients who Underwent Liver Transplantation Due for Hepatocellular Carcinoma

Atilla Bulur[1], Uğuray Payam Hacısalihoğlu[2], Murat Sevmiş[3]

[1]Nazilli State Hospital, Clinic of Gastroenterology, Aydın, Turkey
[2]İstanbul Yeni Yüzyıl University Faculty of Medicine, Gaziosmanpaşa Hospital, Department of Pathology, İstanbul, Turkey
[3]İstanbul Yeni Yuzyil University Faculty of Medicine, Gaziosmanpaşa Hospital, Department of General Surgery and Transplantation, İstanbul, Turkey

Abstract

Objective: Although the most effective current treatment method for hepatocellular carcinoma (HCC) is liver transplantation (LT), some patients may have a recurrence of HCC after transplantation. In our study, we investigated the laboratory and histopathological factors that we think may predict HCC recurrence before and after transplantation in patients who underwent LT due to HCC.

Methods: Pre and post transplantation clinical, laboratory, imaging and histopathological data of 66 patients who underwent LT for HCC approximately 2017-2020 in our hospital were retrospectively reviewed. The patients who developed recurrence were examined in detail.

Results: Recurrence developed in seven (10.61%) of 66 patients who underwent LT due to HCC. The mean age of the patients with and without relapse was 60.14 and 58.63 years, respectively. Most patients who underwent LT were men, and all patients with recurrence were men. In patients with recurrence, maximum tumor diameter measured macroscopically (5 cm; 2.7 cm, p=0.002) and presence of lymphovascular invasion (42.9%; 10.2%, p=0.048) were significantly higher than those without recurrence. Serum alpha feto protein (AFP) values at postoperative 3rd, 6th, and 9th months were significantly higher (p=0.001, p=0.004, p<0.001, respectively) in the recurrence group.

Conclusion: In our study, it was determined that increasing perioperative tumor size, presence of lymphovascular invasion and postoperative increased AFP values can predict HCC recurrence.

Keywords: Hepatocellular carcinoma, liver transplantation, recurrence

INTRODUCTION

Hepatocellular carcinoma (HCC), which is the fifth most common tumor worldwide that develops because of many diseases affecting the liver. HCC-related deaths are at the 3rd rank of cancer-related deaths and are an important health problem worldwide (1-3). Liver transplantation (LT) is one of the accepted treatment modalities for HCC. The Milan criteria are currently accepted as the gold standard criteria for the determination of LT candidates from HCC patients (4). It is a method that can be applied in inoperable HCC patients irrespective of the degree of liver function (5). Moreover, it has a therapeutic effect on the underlying pathology and hence, affects the prognosis by decreasing the risk of recurrence or de novo HCC (6,7). In a paper published in 1996, Mazzaferro et al. (8) proposed the Milan criteria as a means of determination of patients suitable for LT in cases where the tumor is ≤5 cm or less than three tumors ≤3 cm in diameter in the absence major vessel invasion or extrahepatic tumor dissemination. The overall survival rates after LT for HCC

Address for Correspondence: Atilla Bulur, Nazilli State Hospital, Clinic of Gastroenterology, Aydın, Turkey
Phone: +90 256 312 00 00 **E-mail:** atillabulur@hotmail.com **ORCID ID:** orcid.org/0000-0001-8089-7740

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range from 65% to 80% at 5 years for patients fulfilling these criteria (9-11).

The attempt to broaden the criteria is predicated on the postulation that the Milan criteria may be too strict, leading to the possibility of a significant number of patients that could benefit from LT being excluded. If we adhered to the Milan criteria, only about 6% of HCC patients would be considered eligible for LT (12,13). Recurrence has not been demonstrated ubiquitously in HCC cases that do not meet the Milan criteria. Furthermore, a premise has been put forward the that a significant segment of those patients could also potentially benefit from LT without affecting HCC recurrence rates. It has also been suggested that many of these patients could benefit from LT without affecting their HCC recurrence rate (13-15).

HCC recurrence has been reported in around 10% of patients after LT due to HCC (16,17). It has been reported that recurrence of HCC may develop from extrahepatic metastases that were missed or undetected before transplantation or by accommodation of circulating tumor cells in organs during the peritransplant period. Studies have reported that tumor burden (volume), maximum tumor size, and alpha feto protein (AFP) level, which are the main tumor markers of HCC, are useful in predicting recurrence after transplantation (18,19). In our study, we investigated clinical, laboratory, imaging and histopathological factors that may indicate recurrence before and after transplantation in patients who underwent LT due to HCC.

METHODS

In our study, the clinical, operational, laboratory, imaging and histopathological data of patients who underwent LT between 2017 and 2020 in the organ transplant unit of our hospital with a diagnosis of HCC and that were followed up by our gastroenterology clinic were retrospectively reviewed. Patient consent and Istanbul Yeni Yuzyil University Faculty of Medicine Ethics Committee approval were obtained in our study (decision date and number: 13.08.2020/033). Patients with recurrence HCC were determined according to laboratory, imaging and/or histopathological (liver biopsy) criteria. Patients who developed mortality due to recurrence or any other reason was excluded from the study.

Statistical Analysis

The research data were uploaded and evaluated using IBM SPSS 25 (IBM Statistical Package for Social Sciences). Descriptive statistics of categorical variables are presented as numbers and percentages. Descriptive statistics of numerical variables are presented as mean (±) standard deviation for normally distributed variables and as median (min-max) for non-normally distributed variables. In a comparison of categorical variables, cross tables were used and "Pearson chi-square test" and "Fisher's Exact test" were applied. The conformity of numerical variables to normal distribution was examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). "Independent samples t-test" was used as the statistical method for determining the statistical significance between groups for variables found to conform to normal distribution and "Mann-Whitney U test" was used for variables that were not normally distributed. The homogeneity of the variances of normal variables between the groups was evaluated with the "Levene test". "Cohen's Kappa coefficient" was used in the categorical variables to determine the agreement between the two measurements. Since the normal distribution is not observed in numerical variables, "Spearman Rank coefficient correlation coefficient (Spearman's rho)" was used. Statistical significance levels were accepted as $p<0.05$ and $p<0.001$.

RESULTS

In our study, 6 (9.1%) of 66 patients who underwent LT due to HCC were female, while 60 (90.9%) were male. LT had been applied to all patients more than a year ago. Recurrence was observed in 7 (10.6%) of the patients, whereas no recurrence was observed in 59 (89.4%) patients. The mean age of patients with relapse was 60.14±3.93 (56-67), while the average age of patients without recurrence was 58.63±8.71 (18-70) years. There was no statistically significant difference between the study groups in terms of age. All patients with recurrence were men. There was no statistically significant difference between the study groups in terms of gender. Post-transplant recurrence times ranged from 12-58 months, with a mean recurrence time of 35.43±17.89 months (Table 1).

Considering the etiology of the patients with recurrent disease, 85.7% of them (6 patients) had chronic hepatitis B (HBV)-related HCC. Only 1 patient (14.3%) was found to have chronic hepatitis C-related HCC. Most patients without recurrence (28 patients, 47.5%) also consist of HCC patients developing on the basis of HBV. There was no statistically significant difference between the recurrence and etiological conditions of the patients. No statistically significant difference was found between the Child-Pugh score (9.14 and 8.41) and model for end-stage liver disease; (MELD; 13.14 and 12.88) mean scores of patients with and without recurrence. While 42.9% (3 patients) of patients with recurrence were within Milan's criteria, 57.1% (4 patients) were beyond the Milan criteria. While 74.6% of the patients without

recurrence (44 patients) were within Milan criteria, 25.4% (15 patients) were beyond Milan criteria. There was no statistically significant relationship between patients relapse status and Milan criteria status (Table 1).

According to the histopathological examinations of the patients, no statistically significant relationship was found between patients with recurrence and without recurrence in terms of localization (unilobuler, bilobular). The mean maximum tumor diameter measured in the operation materials of patients with recurrence was 6.29±2.94 cm, while those without recurrence was 3.09±2.14 cm. We observed that the maximum tumor diameters of patients with recurrence were higher than those without recurrence, and this difference was found to be statistically significant (p=0.002). In patients with recurrent disease, lymphovascular invasion was observed in 42.9% (3 patients), whereas no lymphovascular invasion was observed in 57.1% (4 patients). Most of the patients without recurrence (53 patients) did not have lymphovascular invasion, and a statistically significant relationship was found between their recurrence status of the patients' and their lymphovascular invasion status (p=0.048). There was no perineural invasion in any patient with recurrent disease. In patients without recurrence, only 2 patients had perineural invasion. There was no statistically significant relationship between the presence of recurrence and the presence or absence of perineural invasion. There was no correlation between the histopathological tumor grades, pathological stages according to TNM (T for tumor size and local cancer invasion; N for nearby lymph node metastasis; and M for distant metastasis) classification, surgical margin status and recurrence. Additionally, all patients with and without recurrence had negative lymph nodes (Table 2).

We observed that the AFP values of patients with recurrent disease were significantly higher than those without recurrence. All patients with and without recurrence completed a post-operative year without mortality. Additionally, when the median of these AFP values were compared according to the recurrence status of the patients, a statistically significant difference was found in all months (3rd, 6th, and 12th months) except month zero (AFP 0), p_{AFP90}=0.001, p_{AFP80}=0.004, p_{AFP60}<0.001 (Table 3).

DISCUSSION

HCC is one of the most common and fatal tumors in the world. LT is the most effective treatment method in HCC treatment. LT is a complicated surgery that can be performed in centers with experienced multidisciplinary clinics and requires pre-transplant patient selection and close follow-up to prevent recurrence and mortality. Milan criteria are used in patient selection to achieve low recurrence and high survival rates in HCC patients who undergo LT, in many centers (8). These criteria are obtained by

Table 1. Demographic and clinical characteristics of the patients

		Patients with recurrence	Patients without recurrence	p
Age (years)		60.14±3.93	58.63±8.71	0.631
Gender	Female	0 (0)	6 (10.2)	0.496
	Male	7 (100)	53 (89.8)	
Time relapsed after transplant (months)		35.43±17.89	30.59±16.47	0.469
CHILD score		8 (5-14)	8 (5-13)	0.447
MELD score		12 (10-17)	12 (8-24)	0.798
Milan	Within	3 (42.9)	44 (74.6)	0.099
	Beyond	4 (57.1)	15 (25.4)	

CHILD score: Child-Pugh score, MELD score: Model for end-stage liver disease

Table 2. Comparison of the histopathological characteristics of the patients

Histopathological features		Patients with recurrent disease	Patients without recurrent disease	p
Maximum tumor diameter (cm)		5 (3.5-12)	2.7 (0.5-13)	0.002
Lymphovascular invasion	Yes	3 (42.9)	6 (10.2)	0.048
	No	4 (57.1)	53 (89.8)	
Perineural invasion	Yes	0 (0)	2 (3.4)	0.795
	No	7 (100)	56 (96.6)	
Localization	Unilobular	5 (71.4)	46 (78.0)	0.504
	Bilobular	2 (28.6)	13 (22.0)	

Table 3. Comparison of preoperative and postoperative (3.6 and 12 months) AFP values (ng/mL)			
	Patients with recurrent disease	**Patients without recurrent disease**	**p**
AFP 0	19 (2.9-4019)	9.4 (1-655)	0.411
AFP 90	8.7 (2.30-1502)	1.75 (0.75-11)	0.001
AFP 180	3.5 (1.27-11870)	1.6 (0.60-11)	0.004
AFP 360	90.4 (18.5-50000)	1.59 (0.75-13.10)	<0.001
AFP: Alpha feto protein			

a simple assessment based on tumor number and size, however factors that impact recurrence and survival apart from the Milan criteria, have also been investigated in many studies (18-20). HCC recurrence after LT is one of the undesirable consequences of this treatment method (21). In our center, LT can be applied to patients beyond the Milan criteria same as in some transplant centers, when necessary. We retrospectively examined the clinical, laboratory, imaging and histopathological data of 66 patients who underwent LT due to HCC in our gastroenterology outpatient clinic, and we wanted to obtain data that would enable us to predict recurrence in 7 patients who developed recurrence. In the literature, the recurrence rate among HCC patients who underwent LT is around 10%. The recurrence rate was 10.6% in our study. In our study, all patients with recurrence were alive. In similar studies in the literature, the mean survival time of patients after recurrence was reported to be 8-24 months (16-18,22-25). In our study, 6.38% of patients within Milan and 21.05% of patients beyond the Milan criteria had recurrent disease. Being beyond the Milan criteria increases the risk of recurrence in accordance with similar studies (26,27). The mean age of our patients with recurrence was 60.14 years, the mean age of patients without recurrence was 58.63 years. No statistically significant difference was found between the ages of the patients (p=0.631). While all the patients with recurrence were male, 10.2% of the patients without recurrence were female and 89.2% of them were male (Table 1). Although there was no statistically significant difference between the study groups in terms of gender (p=0.496), it is striking that most our patients who underwent LT with a diagnosis of HCC and all of those with recurrence were male. In our study, HCC recurrence was most frequently observed in patients with HCC developing on the basis of HBV related cirrhosis (85.7%). In a study conducted in our country, it was reported that in patients with HCC developing on the basis of HBV, recurrence rate increased and the survival rate decreased (28). Apart from these criteria, it has been shown in many studies that tumor size alone increases the risk of recurrence (29). In our study, the mean maximum tumor size was 6.29±2.94 cm in patients with recurrence, while it was 3.09±2.14 cm in patients without recurrence. A significant difference was found between both groups (p=0.002). In our study, the of lymphovascular invasion was observed in 3 patients (42.9%) in the recurrence group, whereas it was observed in 6 patients (10.2%) in the non-recurrence group. A significant difference was found between the two groups (p=0.048) (Table 2). We observed that the increase in maximum tumor size and the presence of vascular invasion played a significant role in the development of recurrence, and this result was found to be consistent with other studies (8,12,28). Although it was not statistically significant, according to the TNM classification, 3 (42.9%) of the patients with relapse were in the T2 stage, 3 (42.9%) were in the T3 stage, while most patients without recurrence were in the T1 and T2 (39% and 47.5%) stages. It has been reported that serum AFP level measured in the pretransplant period is a determinant of recurrence and survival after transplantation. Studies have found that patients with high AFP levels have higher rates of mortality and/or HCC relapse (29-31).

Of note, AFP values more than 1000 ng/mL before LT have been associated with the risk of HCC recurrence after LT (32-34). In our study, the preoperative AFP values (AFP 0) and posttransplant 30, 90, 180 and 360 day AFP values of the patients with recurrence were found to be higher than those of the patients without recurrence. AFP values were found to be statistically significant between 90, 180, and 360 days (Table 3).

Recurrence developed in 10.6% of the patients who underwent LT. Mortality did not occur in these patients, and rejection did not develop before recurrence. This may be related to patient selection before transplantation and close follow-up of our immunosuppressive treatment after transplantation. Clinical studies have revealed that the use of mammalian target of rapamycin (mTOR) inhibitors in the treatment during the transplant period, because to their anticancer efficacy, reduces post transplant HCC recurrence and increases survival (35-38). In our study, mTOR inhibitors (everolimus) treatment was initiated for each patient after the third month post-transplantation, to prevent recurrence.

Study Limitations

There are more prospective similar studies in the literature with a higher number of cases and follow-up time, which constitutes a limitation for our study. Conducting multi-center and prospective studies with a larger number of patients would yield more significant results in the future.

CONCLUSION

Although LT was applied to 66 patients due to HCC in approximate four years at our center, we think that this is a considerable number since we only included LTs with the indication of HCC in our study. In our study, among the factors that increase cancer recurrence; the maximum diameter of the tumor, presence of lymphovascular invasion and post transplant increasing AFP values were found to be statistically significant. Additionally, having a chronic HBV related HCC, multifocal tumor and poor differentiation were found to be important factors for recurrence.

Ethics

Ethics Committee Approval: Istanbul Yeni Yuzyil University Faculty of Medicine Ethics Committee approval were obtained in our study (decision date and number: 13.08.2020/033).

Informed Consent: Patient consent obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.B., U.P.H., M.S., Concept: A.B., Design: A.B., Data Collection or Processing: A.B., U.P.H., M.S., Analysis or Interpretation: A.B., U.P.H., M.S., Literature Search: A.B., U.P.H., Writing: A.B.

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