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Original Article

The impact of tumor localization on prognosis of the patients following liver transplantation for hepatocellular carcinoma

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Abstract

Aim: Hepatocellular carcinoma usually occurs in the setting of liver cirrhosis and therefore, resection is not possible in majority of the cases. Orthotopic liver transplantation (OLS) is a gold standard treatment option in hepatocellular carcinoma. The aim of the present retrospective study was to evaluate the prognosis of hepatocellular carcinoma localized in left or right side of the liver in patients who underwent OLS.

Materials and Methods: 120 patients received OLS for hepatocellular carcinoma between 2007 and 2018 in the institute of liver transplantation. Tumors that were centrally located were excluded from the analysis. The remaining 104 patients were divided into two groups; Group 1 (right lobe, n=85 [81.7%]), Group 2 (left lobe, n=19 [18.3%]). The clinical and demographic data of the patients along with preoperative laboratory values such as alpha fetoprotein (AFP), gamma-glutamyl transpeptidase (GGT) and thrombocyte count were retrospectively evaluated.

Results: The Median age in Group 1 and 2 were 54 (4-72) and 50.5 (37-68) years, respectively. Preoperative AFP levels in Group 1 and 2 were 9.25 (1-10800) ng/ml and 13 (1.5-317) ng/ml, respectively. The Model for end stage liver disease (MELD) scores in Group 1 and 2 were 12 (6-52) and 9 (6-21), respectively. None of the clinical, demographic and laboratory values along with disease-free survival, early mortality and recurrence were significantly different among the study groups (p>0.05).

Conclusions: Although there is a big discrepancy in terms of patient's numbers in right and left-sided tumors, our data failed to show any survival difference among the groups. Further studies, especially in hepatocellular carcinoma beyond the Milan criteria, are needed to validate our results.

Keywords: Hepatocellular carcinoma; liver; milan criteria; transplantation

INTRODUCTION

Hepatocellular carcinoma (HCC) is an aggressive malignancy and the most prevalent primary malignancy of liver. It is the second leading cause of death attributed to cancer. Resection and liver transplantation are considered the curative treatment options. In the recent years, treatment of HCC has been improved and an increasing number of patients can survive longer with a variety of therapeutic methods such as transcatheter artery chemoembolization (TACE), percutaneous ethanol injection, radiofrequency cytoablation, and liver resection. Orthotopic liver transplantation (OLS) is another excellent treatment for HCC patients. It removes the liver along with hepatic tumor and also treats underlying cirrhosis (1, 2). The five-year survival rates reached 75% in well-selected candidates and a consensus was reached on by considering the Milan criteria (MC) for cadaveric transplantation. These results are similar to the expected survival rates in patients undergoing transplantation for cirrhosis without HCC (3).

The literature lacks research data regarding site of HCC as the prognostic factor of OLS. The aim of the present study was to evaluate which site of tumor affects surgical outcomes after OLS for patients with HCC.

MATERIALS and METHODS

This retrospective study was conducted at Inonu University Turgut Ozal Medical Center Institute of Liver Transplantation in accordance with the ethical standards of the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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The database searched for patients underwent OLS for HCC between 2007 and 2018 at the institute. Initial search delivered 120 patients received OLS for HCC. All of the patients underwent surgery in line with MC and listed for liver transplantation based on model of end stage liver disease (MELD) score. From those, tumors that were centrally located were excluded from the analysis. The remaining 104 patients were divided into two groups; Group 1 (right lobe, n=85 [81.7%]), Group 2 (left lobe, n=19 [18.3%]).

The clinic and demographic characteristics of the patients along with preoperative laboratory values were included in the statistical analysis. The diameter of tumors and number of deposits were determined according to the histopathological analysis of explants. Also, the rate of tumor differentiation and venous invasion were identified based on pathological specimen analysis.

At Turgut Ozal Medical Center Institute of Liver Transplantation, following tests are performed as a standard pre-operative and post-operative protocol for patients with HCC. Preoperatively, multi-slice computed tomography (MSCT), magnetic resonance imaging (MRI) and [18F] Fluorodeoxyglucose positron emission tomography (PET/CT) are performed for the delineation of disease status. In the post-transplant follow-up period, monthly AFP, abdominal ultrasound once in every 3 months and MSCT once in every 6 months are performed for the initial 2 years. In the post-operative 2 to 5 years, annual MSCT is performed. In post-transplant patients with high AFP levels, MSCT, MRI and PET/CT are performed (4).

Statistical analysis was performed using SPSS software (SPSS version 20.0, SPSS Inc., Chicago, IL, USA). All data were checked for normal distribution. The grouping variables were expressed as "number (percentage)". Parametric values were given as "mean±standard deviation" and non-parametric values, "median (range)". The Mann-Whitney U test and two independent samples t-test were used for quantitative variables between binary groups. The Chi-square statistic was used for the comparison of nominal variables. Statistical significance was accepted at 0.05.

RESULTS

Of all, in 85 (81.7%) of the patients the tumors were located in the right lobe (Group 1) and in 19 (18.3%) in the left lobe (Group 2). In group 1, the female/male ratio of the patients was 11/74. The median age of the patients was 54 (4-72) years. The median follow-up time was 648 (0-4014) days. In the preoperative period, the median levels of alfa-fetoprotein (AFP) and MELD scores were found as 9.25 (1-10800) ng/mL and 12 (6-52), respectively. The median diameter of tumors was 3 (1-5) cm and all of the patients harbored one tumor deposit. Of all the patients, 52 (61.1%) had chronic liver disease secondary to hepatitis B virus (HBV). One patient had chronic liver disease due to alcohol accompanied with HBV. Cadaveric liver transplantation was performed in 10 patients (11.7%). Tumors were well differentiated in 40 (47.1%), moderately differentiated in 39 (45.9%) and poorly differentiated in 5 (5.9%). Venous invasion was not detected in 62 (72.9%) patients. The median number of platelet count and GGT levels of the patients were 88.500 (19.000-360.000) cells/mm3 and 63 (13-341) IU/mL, respectively. Recurrence was observed in 2 (2.4%) patients. The median time of disease-free survival was 648 (0-4014) days. Early mortality was observed in 14 (16.5%) patients.

Table 1. The table demonstrates clinical, demographic and outcomes of patients with hepatocellular carcinoma underwent orthotopic liver transplantation

Variables	Results		P value
	Group 1 (n=85)	Group 2 (n=19)	
Age, y, median (range)	54 (4-72)	50.5 (37-68)	.386
Gender, female/male	11/74	2/17	-
MELD score, median (range)	12 (6-52)	9 (6-21)	.456
Hepatitis B virus association, n (%)	52 (61.1)	11 (57.9)	.234
Preoperative AFP levels, ng/mL, median (range)	9.25 (1-10800)	13 (1.5-317)	.732
Platelet count, cells/mm3, median (range)	88.500 (19.000-360.000)	111.500 (41.000-294.000)	.554
Gamma-Glutamyl transferase level, IU/mL , median (range)	63 (13-341)	76 (16-187)	.580
Cadaveric graft rate, n (%)	10 (11.7)	3 (15.9)	.670
Tumor diameter, cm, median (range)	3 (1-5)	3 (2-4)	.235
Number of tumor deposit, median	1	1	.087
Moderate-Poor tumor differentiation rate, n (%)	44 (51.8)	8 (42)	.885
Venous invasion rate, n (%)	23 (27.1)	3 (15.8)	.532
Early mortality rate, n (%)	14 (16.5)	5 (26.3)	.486
Follow-up period, d, median (range)	648 (0-4014)	428 (1-3684)	.652
Recurrence rate, n (%)	2 (2.4)	1 (5.2)	.235
Disease-Free survival, d, median (range)	648 (0-4014)	428 (1-3684)	-

In group 2, the female to male ratio was 2/17. The median age of the patients was 50.5 (37-68) years. The median follow-up time was 428 (1-3684) days. In the preoperative period, the median levels of AFP and MELD scores were 13 (1.5-317) ng/mL and 9 (6-21), respectively. The median diameter of tumors was 3 (2-4) cm and the median number of tumors was 1. 11 patients (57.9%) had chronic liver disease secondary to HBV. Cadaveric liver transplantation was performed in 3 (15.9%) patients. Tumors were well differentiated in 10 (52.6%), moderately differentiated in 7 (36.8%) and poorly differentiated in 1 (5.2%), and no venous invasion was detected in 16 (84.2%) patients. The median number of platelet count and GGT levels were 111.500 (41.000-294.000) cells/mm3 and 76 (16-187) IU/mL, respectively. Recurrence was observed in 1 (5.2%) patient. The median time of disease-free survival was 428 (1-3684) days. Early mortality was observed in 5 (26.3%) patients.

None of the clinic, demographic and preoperative laboratory parameters were significantly different between the study groups ($p>0.05$). In addition, no statistically significant difference was observed between Group 1 and Group 2 in terms of recurrence, disease-free survival and mortality rate (Table 1).

DISCUSSION

The primary objective of this study was to evaluate the prognosis of patients who underwent OLS for HCC while comparing site of tumor origin. HCC represents 80% of primary liver malignancies. Also, it is the second cause of cancer-related deaths all over the world (5, 6).

There are several important risk factors for the development of hepatocellular carcinoma. Among these, hepatitis B virus (HBV) infection and chronic hepatitis C virus (HCV) infection are the most common causes (7, 8). In an analysis of nearly 770.000 HCC cases worldwide in 2012, more than 50 percent of the cases were attributed to chronic HBV infection and 20 percent of HCV. Most HCC cases occur in eastern Asia and sub-Saharan Africa where the major risk factors are HBV and aflatoxin exposure, while HCV found to be the primary risk factor in the USA, Europe, and Japan (9).

For the treatment of early-stage HCC, liver transplantation constitutes the best option, since it provides treatment of the tumor and the causing disease. Following widespread implementation of MC in 1996, liver transplantation has been acknowledged as the best curative option for patients with HCC. The results of initial studies indicated that if OLS is performed when the disease is in the early-stage (1 nodule smaller than ≤ 5 cm or ≤ 3 lesions, none of them are bigger than 3 cm and without gross vascular invasion, metastases or nodal disease), the four-year survival was reportedly 75% while recurrence rates were below 10-15%. The outcomes are not distinct from those seen in non-HCC cirrhotic subjects (10). Good clinical outcomes have also been achieved in cases with extended criteria (11, 12). However there has not been reached consensuses on expansion of OLS criteria for HCC (13).

Although OLS provides prominent benefit for HCC, as a result of organ shortage, determination and management of surgical candidates continues to be a fundamental question. Recurrence of HCC after OLS is the most important cause of post-transplant mortality (14). HCC tumor recurrence following transplantation has been estimated to be approximately 8-20% (15).

Actually, besides size and number of HCC deposits, there are other factors affecting surgical outcomes following OLS. For instance, either number or size, these are not always related to poor prognosis, vascular invasion and biologic characteristics of the tumor (13). Hence, beyond MC, identification of additional factors needed to decrease possibility of tumor recurrence and rectify selection criteria. According to histological analysis of explanted livers, tumor characteristics such as vascular invasion, differentiation rate and satellite lesions could have impact on occurrence of HCC recurrence (16). Nevertheless, these parameters are not suitable to be used in the pre-transplant setting.

In this work up, the two primary outcomes of interest are HCC recurrence and patient survival after OLS. None of the parameters were significantly different between the study groups (right side vs. left side HCC groups). The present study failed to demonstrate any effect of tumor location within the liver (right vs. left side tumor) on either tumor recurrence or survival. We believe that this study is the first to report the effects and data of localization on tumor characteristics and patient prognosis in OLSs performed due to HCC.

A plethora of studies have been published to identify additional factors affecting outcome of OLS in these patients to refine the current selection criteria. Of the biological markers studied, AFP is the most commonly used prognostic marker for invasion and treatment decisions for patients with HCC. It has been shown that it correlates significantly with recurrence after transplantation (17). In view of this evidence, new transplant selection criteria that include AFP have been investigated (18,19). Lee and associates demonstrated the clinical impact of PET/CT in patients who underwent living-donor liver transplantation. 52.5% of the patients had HCC staged beyond MC according to pathological analysis. When patients with HCC beyond MC (whom PET/CT negative, tumor size of <10 cm) compared to those with HCC within MC, similar overall and disease-free survival were observed (20). In another study with recipients by Song et. al., it was reported that the combination of AFP and 18F-FDG PET/CT resulted more accurate prediction of prognosis than MC (21). At the institute, we observed similar results to Song et al.'s study and added PET/CT to the HCC protocol. Pre-transplant loco-regional therapy (LRT), including TACE and radiofrequency ablation benefit to reduce post-transplant recurrence remains unclear. In clinical practice, LRT has been regarded as a bridge to OLS whilst controlling tumor growth. However, the usefulness of LRT has not been clarified in this regard. In a meta-analysis, various articles evaluating LRT in patients with

HCC were examined and they lacked a clear demonstration of benefit on recurrence and survival in post-transplant patients (22). Considering other non-tumor factors, higher calculated MELD score in recipients was reported to be linked to worse post-transplant survival (14).

CONCLUSION

While our study failed to demonstrate any effect of tumor location within the liver (right vs. left side tumor) on either tumor recurrence or survival, interpretation of published data on the impact of the pre-transplant factors that significantly affects outcome and considering it into the selection criteria is necessary for optimal results to be achieved.

Conflict of interest: The authors declare that they have no competing interest.

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Ethical approval: This retrospective study was approved by Inonu University Clinical Research Ethics Committee (2020/1227).

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