# Oncological Outcomes of Hepatic Resection vs Transplantation for Localized Hepatocellular Carcinoma

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ABSTRACT

Background. Scarce data are available comparing outcomes of hepatic resection vs orthotopic liver transplantation (OLT) for localized hepatocellular carcinoma (HCC) patients both meeting and exceeding the Milan criteria. This study compared the clinical and oncological outcomes of patients undergoing hepatic resection vs transplantation localized HCC.

Method. Between January 2005 and February 2017, clinical and oncological outcomes of patients who underwent liver resection (n = 38) vs OLT (n = 28) for localized HCC were compared using a prospectively maintained database.

Results. A total of 66 patients (with a median age of 62) who met the study criteria were analyzed. Comparable postoperative complications (13.2% vs 28.6%, $P$ = .45) and perioperative mortality rates (7.9% vs 10.7%, $P$ = .2) were noted for the resection vs OLT groups. While Child-Pugh Class A patients were more prevalent in the resection group (78.9% vs 7.1%, $P$ = .0001), the rate of patients who met the Milan criteria was higher in the OLT group (89.3% vs 34.25, $P$ = .0001). Recurrence rates were 36.8% in the resection group and 3.6% in the OLT group at the end of the median follow-up period (32 vs 39 months, respectively). The HCC-related mortality rate was significantly higher in the resection group (39.5% vs 10.7%, $P$ = .034).
However, a subgroup analysis of patients who met the Milan criteria revealed similar rates of recurrence and HCC-related mortality (15.4% vs 8%, $P$ = .63). Based on logistic regression analysis, number of tumors ($P$ = .034, odds ratio: 2.1) and "resection"-type surgery ($P$ = .008, odds ratio: 20.2) were independently associated with recurrence.

Conclusion. Compared to liver transplantation, hepatic resection for localized hepatocellular carcinoma is associated with a higher rate of recurrence and disease-related mortality.

HEPATOCELLULAR carcinoma (HCC) is the third leading cause of cancer-related mortality worldwide [1]. As the most important etiologic factor for HCC, there has been a great deal of attention paid to the hepatitis B virus because of its rising prevalence and the financial burden it places on the healthcare system in Turkey [2].

Although a broad spectrum of treatment modalities consisting of resection, transplantation, locoregional treatments (eg, radiofrequency ablation, transarterial chemoembolization, and transarterial radioembolization), and systemic chemotherapy has been established for HCC, resection and liver transplantation have been theoretically regarded as the only options with potentially curative intent [3–6]. Compared to liver resection, superior outcomes associated with transplantation have been reported in recent years due to treating the underlying disease in addition to tumor removal [7,8]. Nevertheless, because of the shortage of cadaveric organ donation and common sense related to the

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**Table 1. The Distribution of Patient- and Disease-related Data**

| | Resection | | Transplantation | | |
|---|---|---|---|---|---|
| | n | % | n | % | *P* |
| Sex | | | | | |
| Male | 35 | 92.1 | 24 | 85.7 | .446 |
| Female | 3 | 7.9 | 4 | 14.3 | |
| Etiology of cirrhosis | | | | | |
| Alcohol | 2 | 5.3 | 1 | 3.6 | .224 |
| Hepatitis B | 24 | 63.2 | 24 | 85.7 | |
| Hepatitis C | 3 | 7.9 | 1 | 3.6 | |
| Cryptogenic | 9 | 23.7 | 2 | 7.1 | |
| Ascites | 11 | 28.9 | 21 | 75.0 | .0001 |
| Encephalopathy | 2 | 5.3 | 13 | 46.4 | .0001 |
| Child score | | | | | |
| A | 30 | 78.9 | 2 | 7.1 | .0001 |
| B | 6 | 15.8 | 14 | 50.0 | |
| C | 2 | 5.3 | 12 | 42.9 | |
| Preoperative therapeutic intervention | | | | | |
| No | 31 | 81.6 | 12 | 42.9 | .008 |
| RF | 0 | 0.0 | 3 | 10.7 | |
| TACE | 5 | 13.2 | 9 | 32.1 | |
| TACE + RF | 2 | 5.3 | 4 | 14.3 | |
| Bilobar distribution | 2 | 5.3 | 2 | 7.1 | 1.000 |
| Multicentricity | 12 | 31.6 | 9 | 32.1 | 1.000 |
| Rate of meeting Milan criteria | 13 | 34.2 | 25 | 89.3 | .0001 |

Abbreviations: RF, radiofrequency ablation; TACE, transarterial chemoembolization.

health status of living donors, rendered resection is still a valid therapeutic option for localized HCC.

As the Milan criteria is considered restrictive by a number of centers, the San Francisco and Barcelona criteria are most widely accepted systems for suggesting treatment allocation for patients with localized HCC [9–12]. While salvage resection can be offered to HCC patients on the waiting list for LT, resection can be an alternative to those with aggressive tumors who do not meet the Milan criteria. Technical ease has been achieved in both liver resection and transplantation using an anesthesia strategy with low central venous pressure, portal inflow techniques, and an increasing amount of new coagulants [13–16]. However, post-resection or post-transplant long-term overall survival and recurrence rates are currently being debated in the literature [4,12,16–19].

With regard to localized HCC, data determining which curative intent therapies to provide patients are limited and there is no consensus on which guideline is superior. In this study, we aimed to compare outcomes of patients undergoing liver resection vs transplantation for patients with localized HCC.

## METHOD

Between January 2005 and February 2017, patients who underwent liver resection (n = 38) vs orthotopic liver transplantation (OLT) (n = 28) for localized HCC were compared using a prospectively maintained database. Following approval by the internal ethical committee of Cukurova University, written informed consent was obtained by all patients enrolled in the study. Patients who have mixed-type pathology (HCC with cholangiocarcinoma) based on

**Table 2. Comparison of Preoperative Biochemical, Tumor-related, and Functional Scoring Systems of the Liver.**

| | Resection | Transplantation | *P* |
|---|---|---|---|
| Age (y) | 62.8 ± 12.8 | 58.5 ± 6.1 | .100 |
| Preoperative creatinine | 0.96 (0.51–1.63) | 0.74 (0.2–1.4) | .0001 |
| INR | 1.18 ± 0.16 | 1.40 ± 0.24 | .0001 |
| Bilirubin | 1.29 (0.36–14.3) | 1.32 (0.55–4.3) | .432 |
| Albumin | 3.42 ± 0.7 | 3.16 ± 0.6 | .143 |
| AFP | 69 (2–47523) | 14 (1–15323) | .245 |
| Child score | 6 (4–11) | 8 (5–11) | .0001 |
| Number of tumors, median | 1 (1–4) | 1 (1–4) | .786 |
| Maximal tumor diameter | 6.5 (1–17) | 3.8 (1.4–10) | .006 |
| Total tumor diameter | 8 (2–23) | 4 (1.4–10) | .009 |
| MELD score | 10 (6–24) | 15 (6–24) | .006 |
| Sodium level | 135.9 ± 3.5 | 133.9 ± 3.8 | .035 |

Abbreviations: AFP, alpha fetoprotein; INR, international normalized ratio; MELD, Model for End-Stage Liver Disease.

**Table 3. Postoperative Complications and Oncological Outcomes**

| | Resection | | Transplantation | | |
|---|---|---|---|---|---|
| | n | % | n | % | *P* |
| Postoperative complications | 5 | 13.2 | 8 | 28.6 | .209 |
| Recurrence | 14 | 36.8 | 1 | 3.6 | .002 |
| HCC-related mortality | 15 | 39.5 | 3 | 10.7 | .034 |
| Overall mortality | 19 | 50.0 | 7 | 25.0 | .046 |

Abbreviation: HCC, hepatocellular carcinoma.

final pathology examination were excluded (n = 2). The following data were recorded: demographic characteristics, body mass index, blood group, blood sodium, creatinine, bilirubin, albumin, alfa fetoprotein, presence of ascites, and encephalopathy. HCC-related tumor characteristics including number of tumors, maximal tumor diameter, total diameter of multiple tumors, multicentricity, and bi-lobar tumor presence were also recorded. To determine the severity of liver disease, the Model for End-Stage Liver Disease and Child scores were calculated for all cases. Perioperative complications and mortality rates were analyzed.

Milan criteria was used to select patients for liver transplantation as a part of our clinical decision-making process. In order to prevent tumor progress, bridging treatments, including radiofrequency ablation and transarterial chemoembolization, were employed for patients who were expected to be on the waiting list for a long time and who initially met the Milan criteria. The interval between bridging treatment and transplantation, from cadaveric and living donor, was longer than 3 months. Patients with sufficient liver function who met the Milan criteria and those who exceeded the Milan criteria but who were considered eligible for resection undergo segmentectomy or hepatectomy at the discretion of the meeting by multidisciplinary team. R0 resection was achieved in all cases. The same pathology team examined the resection specimens and explants.

The post-transplant/resection patients were followed up through alpha fetoprotein levels, dynamic computed tomography, or magnetic resonance imaging in terms of local or distant recurrence at 3-month intervals within 1 year and 6-month intervals thereafter. For patients who had suspected lesion(s) based on these imaging techniques, further evaluation was performed using bone scintigraphy or a positron emission tomography computed tomography scan. Recurrence, HCC-related mortality, and overall survival rates were analyzed.

## Statistical Analysis

All data were entered and analyzed using SPSS version 17.0 (SPSS, Inc, Chicago, Ill, United States). Continuous variables that followed normal distributions are expressed as mean ± standard deviation and those did not follow normal distributions are summarized in terms of their medians and ranges. Categorical variables were analyzed using the $\chi^2$ test or Fisher's exact test. Comparisons of normally distributed continuous variables were performed using the Student's *t*-test. The Mann-Whitney U-test was used when a variable was not normally distributed. Survival curves were plotted using the Kaplan-Meier method and compared with the log-rank test. Logistic regression analysis was performed to determine independent risk factors for recurrence and HCC-related mortality.

## RESULTS

A total of 66 patients with a male dominance (n = 59, 89.4%) were included in the study. Liver resection and transplantation rates were 57.6% (n = 38) and 42.6% (n = 28), respectively. Table 1 shows patient characteristics and preoperative clinical findings related to the localized HCC. Chronic liver disease secondary to hepatitis B virus constituted the major etiologic factor for HCC development (n = 48, 72.7%). Table 2 demonstrates comparison of preoperative biochemical, tumor-related and liver functional scoring systems between the 2 groups. Maximal tumor diameter was significantly higher in the resection group (6.5 (1-17) cm vs 3.8 (1.4-10) cm, $P = .006$). Compared to the resection group, the Model for End-Stage Liver Disease and Child scores were higher in the transplantation group ($P = .006$ and $P = .0001$, respectively).

Table 3 shows the distribution of postoperative complications and HCC-related and overall mortality rates. Recurrence rates were 36.8% in resection group and 3.6% in OLT group at the end of the median follow-up, 32 vs 39 months, respectively. Similarly, higher HCC-related and overall mortality rates were recorded in the resection group ($P = .034$ and $P = .046$). The mortality rate unrelated to the HCC was higher but statistically non-significant in the transplant group (10.5% vs 14.3%, $P > .05$).

In the subgroup analysis of patients who met the Milan criteria in both groups (resection; n = 13 vs OLT; n = 25), a higher complication rate was observed in the OLT group.

**Table 4. Subgroup Analysis of Patients Who Met the Milan Criteria**

| | Resection | | Transplantation | | |
|---|---|---|---|---|---|
| | n | % | n | % | *P* |
| Postoperative complications | 0 | 0.0 | 8 | 32.0 | .034 |
| Recurrence | 2 | 15.4 | 1 | 4.0 | .265 |
| HCC-related mortality | 2 | 15.4 | 2 | 8.0 | .837 |
| Non-HCC-related mortality | 3 | 23.1 | 4 | 16.0 | .446 |
| Overall mortality | 5 | 38.5 | 6 | 24.0 | .457 |

Abbreviation: HCC, hepatocellular carcinoma.

**Table 5. Logistic Regression Analysis Predicting Recurrence and HCC-related Mortality**

Logistic Regression Analysis for Recurrence

| | B | SE | Wald | df | *P* | Odds Ratio | 95% CI for Odds Ratio | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| Resection vs OLT | 3.006 | 1.126 | 7.128 | 1 | .008 | 20.197 | 2.223 | 183.458 |
| Number of tumors | .784 | .370 | 4.507 | 1 | .034 | 2.191 | 1.062 | 4.521 |
| Constant | −4.786 | 1.331 | 12.928 | 1 | .000 | .008 | | |

Logistic Regression Analysis for HCC-related Mortality

| | B | SE | Wald | df | *P* | Odds Ratio | 95% CI for Odds Ratio | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | Lower | Upper |
| Resection vs OLT | 1.697 | 1.182 | 2.062 | 1 | .151 | 5.456 | .538 | 55.283 |
| Postoperative complication | −3.283 | 1.189 | 7.617 | 1 | .006 | .038 | .004 | .386 |
| Total tumor diameter | .252 | .096 | 6.905 | 1 | .009 | 1.287 | 1.066 | 1.553 |
| Constant | −1.349 | .878 | 2.359 | 1 | .125 | .260 | | |

Abbreviations: CI, confidence interval; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; SE, standard error.

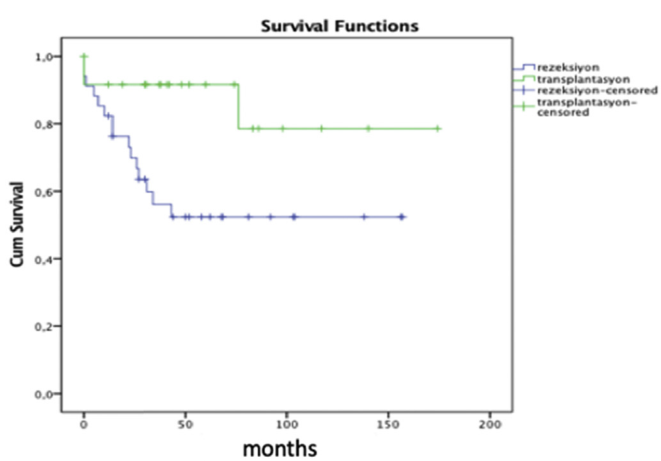
However, similar recurrences and HCC-related and overall mortality rates were noted in both groups (Table 4). Based on the logistic regression model, employing resection vs OLT for HCC and tumor count were independently associated with recurrence. The occurrence of postoperative complications and tumor diameter were found to be independently associated with HCC-related mortality (Table 5).

Figure 1 shows the Kaplan-Meier estimate comparing resection vs OLT in terms of HCC-related mortality. The 2-year survival rate was 76.3% and the estimated 5-year survival rate was 55.0% for the whole population in our study. The 2-year survival rates of the resection and OLT groups were 66.7% and 91.7%, respectively; the 5-year survival estimates for each group were 52.3% and 78.6%, respectively ($P = .02$).

## DISCUSSION

Although the matter of the surgical treatment of localized HCC has been widely discussed in the literature, there has been no consensus on whether resection vs OLT is superior [4,6,13,20]. By accounting for all patient-related variables, the present study revealed that OLT has lower HCC-related mortality and a higher overall survival rate through logistic regression modeling. However, a subgroup analysis of selected patients consisting of those who met the Milan criteria showed similar oncological outcomes.

A number of publications have demonstrated that tumor diameter, alpha fetoprotein level, multinodularity, and the biological properties of tumor affect the development of recurrence [3,4,9,20–22]. While tumor count and the surgical approach of resection were found to be independent




| | Estimate Mean | Std. Error | 95% Confidence Interval | | 2years survival | 5 years survival | P |
|---|---|---|---|---|---|---|---|
| | | | Lower Bound | Upper Bound | | | |
| Resection | 90,8 | 12,6 | 66,2 | 115,5 | % 66,7 | %52,3 | 0.020 |
| Transplantation | 146,7 | 14,9 | 117,4 | 175,9 | %91,7 | %78,6 | |

**Fig 1.** Kaplan-Meier curves demonstrating HCC-related survival.

factors associated with recurrence, occurrence of postoperative complications and tumor diameter were associated with HCC-related mortality. As the foundation of Milan criteria is already based upon tumor diameter and tumor count, our results support the effectivity of the Milan criteria on the prognosis [9]. The negative impact of resection on oncological outcomes can be explained by our preference for resection in patients who exceed the Milan criteria.

Despite similar perioperative mortality or postoperative complication rates, recurrence rates and HCC-associated mortality rates were higher in the resection group compared to the OLT group.

Conceivably, these findings can be attributed to different patient characteristics; presence of ascites and encephalopathy were more prevalent in transplanted patients, who were mainly Child C and eligible for the Milan criteria [23–26]. However, patients undergoing resection were predominantly Child A and beyond the Milan criteria. Although both groups have different distributions of the above-mentioned features, logistic regression modelling addressed these differences, rendering this comparison a reasonable reflection of our HCC-related surgical experience.

Since Mazzaferro et al defined the Milan criteria in 1996 and published favorable long-term results, many centers have begun to use these criteria as a base for transplantation in HCC [9]. Since then, although some centers have regarded the Milan criteria as very restrictive and have used their own criteria by expanding the set with either the San Francisco or Barcelona criteria, which both have gained acceptance in the literature, many centers continue to use the Milan criteria in choosing transplantation for HCC [9–12,27,28]. Hence, we analyzed patients who met the Milan criteria in both the resection and transplant groups as a subgroup in terms of recurrence, morbidity, and mortality. Although the complication rate was high in the transplant group, there was no statistical difference between the 2 groups in terms of recurrence and mortality (HCC-related or non-HCC-related) rates in patients who met the Milan criteria. While Lei et al recently reported that both techniques presented outcomes in patients who met the Milan criteria similar to our study [18], Lee et al, Baccarani et al, and Sapisochin et al reported low post-transplant recurrence and long-term survival rates in patients who met the Milan criteria [7,23,29]. Although some publications found higher morbidity rates among transplanted patients than resected patients with adequate liver function [18], we believe that the relatively high complication rates in transplant patients might be explained by the learning curve period.

Our long-term oncological results are completely in accord with the rates found in the literature. Based upon our clinical experience, while resection is preferred in patients with adequate liver function regardless of whether they met the Milan criteria, we are of the opinion that transplantation might be a suitable option for patients with diminished liver function who meet the Milan criteria. For this reason, transplantation and resection should not be considered conflicting but rather complementary solutions.

The present study has some limitations, including the small number of patients, retrospective design, and the fact that histopathologic parameters were not used, particularly in determining recurrence. When the literature is reviewed, many centers are able to present their own results of either resection or transplantation. However, as our clinic includes both a hepatobiliary surgery unit and a transplant unit, we can present quite long-term results comparing both methods. Logistic regression modeling could eliminate the bias originating from different patient characteristics in each group. From this point of view, this study provides useful data reflecting experience of the same surgical team performing resection vs OLT in the treatment of HCC.

In conclusion, resection can be considered a safe and applicable technique in selected patients; however, OLT has superior oncological outcomes through enabling the removal of a diseased liver. When considering similar outcomes in patients who meet the Milan criteria, functional reserve as well as eligibility for the Milan criteria should be taken into account in the deciding which type of operation to use in the surgical treatment of HCC.

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