ELMER PRESS

Short Communication

Gastroenterol Res. 2021;14(3):190-193

Pre-Transplant Factors Influencing Rates of Hepatocellular Carcinoma Recurrence in Liver Transplant Recipients

Kelly M. Zucker[a, e], Paul A. Gomez[b], Olivia Kezirian[c], Shivang Mehta[d, e]

Abstract

Background: The aim of the study was to determine factors influencing hepatocellular carcinoma (HCC) recurrence in a cohort of patients who underwent liver transplantation (LT) at a large, tertiary-care medical center.

Methods: A total of 132 patients with the diagnosis of HCC at time of transplant were evaluated for HCC recurrence over a 7-year period. Nine patients were found to have HCC recur post-LT.

Results: No significant demographic values were found to indicate recurrence. Pre-LT factors potentially influencing HCC recurrence rates included number of days between HCC diagnosis and date of LT ($P = 0.015$), caudate lobe involvement ($P = 0.019$), increased use of radiation therapies pre-LT ($P = 0.011$), and total number of locoregional therapies (LRT) pre-LT ($P < 0.001$). Post-transplant outcomes demonstrated a significant difference in deep venous thrombosis (DVT) in the recurrent vs. non-recurrent groups ($P = 0.035$).

Conclusions: The prevalence of HCC recurrence in this study was lower than the national average, yet difficulty still exists in predicting pre-LT factors which may influence HCC recurrence rates.

Keywords: Hepatocellular carcinoma; Liver transplantation; Hepatocellular carcinoma recurrence

Manuscript submitted April 26, 2021, accepted June 11, 2021
Published online June 19, 2021

[a]Department of Gastroenterology, University of Arizona College of Medicine Phoenix, Banner University Medical Center-Phoenix, Phoenix, AZ, USA
[b]Department of Internal Medicine, University of Arizona College of Medicine Phoenix, Banner University Medical Center-Phoenix, Phoenix, AZ, USA
[c]Department of Data Management, University of Arizona College of Medicine Phoenix, Banner University Medical Center-Phoenix, Phoenix, AZ, USA
[d]Transplant and Advanced Liver Disease Center, University of Arizona College of Medicine Phoenix, Banner University Medical Center-Phoenix, Phoenix, AZ, USA
[e]Corresponding Authors: Kelly M. Zucker, Banner University Medical Center-Phoenix, Phoenix, AZ, USA. Email: Kelly.zucker@bannerhealth.com; Shivang Mehta, Liver Disease Center, Banner University Medical Center-Phoenix, Phoenix, AZ, USA. Email: shivangmehta.md@gmail.com

doi: https://doi.org/10.14740/gr1402

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common cancer in the USA, and the third most common cause of cancer-related mortality [1]. HCC, especially in early stages, is an indicator of liver transplantation (LT), with or without other contributing comorbidities. The Milan criteria (single tumor 5 cm or less, up to three tumors 3 cm or less, and no macroscopic vascular invasion) has been incorporated into regular LT evaluation for those with HCC [2]. Despite detailed evaluation and selection criteria, there is a wide range of HCC recurrence, with numbers cited anywhere from 6% to 20% [2-4]. The objective of this investigation was to determine if any pre-transplant demographic or HCC characteristics influence rates of HCC recurrence, with a secondary objective to identify differences in post-LT outcomes/complications between the two cohorts.

Materials and Methods

This study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration. After receiving approval from the Institutional Review Board, we retrospectively identified 132 patients who carried the diagnosis of HCC at time of LT from early 2012 to 2019 at Banner University Medical Center in Phoenix, Arizona. This includes patients with active HCC at time of LT, or those previously treated for HCC at time of LT. All patients carried a diagnosis of cirrhosis at time of LT, with etiologies including alcoholic liver disease, hepatitis B, hepatitis C, non-alcoholic fatty liver disease (NAFLD), autoimmune hepatitis, drug-induced liver disease, and primary biliary cirrhosis. Of these 132 patients, nine were noted to have HCC post-LT (recurrence anytime post-LT to the time of analysis), thus providing the two cohorts of HCC recurrent and HCC non-recurrent patients. Baseline demographics were recorded for each group, including: gender, age, body mass index (BMI), donor type, as well as pre-LT HCC information. This HCC information included alpha fetoprotein (AFP) at time of diagnosis of HCC, model for end-stage liver disease (MELD) score, tumor staging, anatomic location within the liver of HCC, treatment modality, and date from diagnosis to transplant. In addition, post-LT outcomes were compared between the two cohorts. Outcomes evaluated included hepatic artery stenosis (HAS), hepatic artery thrombosis (HAT), biliary leak,

Table 1. Pre-transplant HCC Information for the Recurrent and Non-Recurrent Cohorts

HCC pre-transplant information	Non-recurrent (n = 123)	Recurrent (n = 9)	P value
Interval (days) between HCC diagnosis and transplant	503.5 ± 384.9	847.1 ± 635.8	0.015
Interval (days) between listing and transplant	224.9 ± 206.0	341.1 ± 190.3	0.103
MELD at diagnosis	11.9 ± 6.2	11.2 ± 4.9	0.745
AFP at diagnosis	220.6 ± 1,351.4	44.4 ± 105.2	0.698
Initial tumor number	1.4 ± 0.7	1.7 ± 0.7	0.312
Largest tumor measurement (cm)	2.9 ± 1.2	3.1 ± 1.4	0.576
Full Milan criteria	104 (87%)	7 (78%)	0.412
Treatment modality			
Surgical resection	1 (1%)	1 (11%)	0.015
Ablation	34 (28%)	6 (67%)	0.014
Rounds of ablation	1.3 ± 0.8	1.5 ± 0.8	0.509
TACE	87 (71%)	7 (78%)	0.652
Rounds of TACE	1.4 ± 0.7	1.9 ± 0.9	0.072
Radiation	32 (26%)	5 (56%)	0.057
Rounds of radiation	1.1 ± 0.3	1.6 ± 0.5	0.011
Chemotherapy	2 (2%)	-	0.700
Total number of treatments pre-transplant	1.6 ± 1.0	3.6 ± 1.8	< 0.001
Lobe involved			
Left	21 (17%)	1 (11%)	0.643
Right	97 (79%)	7 (78%)	0.939
Quadrate	15 (12%)	-	0.266
Caudate	5 (4%)	2 (22%)	0.019

Means (with standard deviation for continuous values, column percentages for ordinal/categorical variables) for each cohort represented, as well as P values for statistical significance between the cohorts. HCC: hepatocellular carcinoma; MELD: model for end-stage liver disease; AFP: alpha fetoprotein; TACE: transcatheter arterial chemoembolization.

biliary stricture, deep venous thrombosis (DVT), re-exploration, graft rejection, graft failure, re-transplant, and death.

Results

Ordinal and categorical baseline demographic and clinical variables between non-recurrent and recurrent cohorts were calculated using Pearson's Chi-squared test, and continuous values calculated with *t*-tests. P value of < 0.05 was considered significant.

A total of 132 patients carried a diagnosis of HCC and underwent LT from 2012 to 2019 at our institution. One hundred twenty-three patients had no recurrence, while nine of the post-LT patients had HCC recurrence. No significant demographic differences existed for gender, age, BMI, or donor type. There was no significant difference between etiologies of cirrhosis between the recurrent and non-recurrent groups. Pre-LT factors which contributed significantly to HCC recurrence were number of days between HCC diagnosis and LT (P = 0.015), caudate lobe involvement (P = 0.019), increased use of radiation therapy (Y-90 or stereotactic body radiation therapy (SBRT), P = 0.011) and the total number of locoregional therapies (LRT) required pre-LT to remain within Milan criteria (P < 0.001, Table 1).

Post-transplant outcomes showed significant increase in those with HCC recurrence for DVT (P = 0.035) and overall mortality for those in the HCC recurrent cohort (P < 0.001, Table 2).

Discussion

HCC, barring unfavorable characteristics, is a strong indicator for LT. However, HCC recurrence post-LT in our investigation showed significant overall mortality. This is similar to development of recurrence post resection of HCC reducing long-term survival [5]. Pre-LT demographic and HCC characteristics linked to HCC recurrence are still difficult to predict as tumor biology characteristics are not well defined. Our study indicates time from HCC diagnosis to transplant, lobe involvement of original HCC, number and type of pre-LT HCC treatments may influence risk of HCC recurrence. Time to transplant has been one factor that has been used as a surrogate for tumor biology [6]. A significant finding in our study shows the caudate lobe, which can be hypertrophied, may be an area difficult to

Table 2. Post-Transplant Outcomes and Complications for the Recurrent and Non-Recurrent Cohorts

Outcomes/complications	Non-recurrent (n = 123)	Recurrent (n = 9)	P value
HAS	24 (20%)	4 (44%)	0.077
HAT	10 (8%)	-	0.371
Biliary leak	6 (5%)	-	0.496
Biliary stricture	21 (17%)	-	0.174
DVT	6 (5%)	2 (22%)	0.035
Reexploration	13 (11%)	1 (11%)	0.959
Graft rejection	19 (15%)	3 (33%)	0.165
Graft failure	12 (10%)	1 (11%)	0.895
Retransplant	5 (42%)	0 (%)	0.411
Death	19 (15%)	8 (89%)	< 0.001

Means (with percentages for ordinal/categorical variables) for each cohort represented, as well as P values for statistical significance between the cohorts. HAS: hepatic artery stenosis; HAT: hepatic artery thrombosis; DVT: deep venous thrombosis.

treat or an area where LRT for HCC is not fully effective. Also the use of Y-90, SBRT, and increased LRTs increased recurrence presumably as these were markers for larger tumors, but also could indicate worsened tumor biology.

Interestingly, post-LT outcomes in this study indicated a significant difference between the occurrences of DVT in the HCC recurrent group compared to the non-recurrent post-LT population. Overall, about 2.7% of post-LT patients develop a DVT. Many risk factors including prolonged immobilization, post-surgical hypercoagulable state, and defects in the proteins of the coagulation cascade passed from donor to recipient are related to this complication [7]. Preventing triggering factors such as investigation of prior medical history, peripherally inserted central catheter (PICC) placement, prophylactic subcutaneous heparin has been studied to promote prevention of thromboembolic complications [8]. Thus far, little research exists evaluating DVT and other thromboembolic complications in post-LT HCC patients. Our small study highlights an area of future research to determine if post-LT DVT could be an early marker to raise suspicion of future HCC recurrence.

The rate of HCC recurrence nation-wide ranges from 6% to 20% [2-4], and post-LT HCC recurrence rates at our institution were overall on the lower end of national averages at 6.8%. Given this low rate, our investigation was limited due to the overall small number of patients in the HCC recurrent cohort. Given this small sample size, additional factors not measured may have played a significant role in HCC recurrence and adverse post-LT outcomes. Further prospective study on candidate selection, modality and number of LRT, and post-LT follow-up is warranted to further investigate factors influencing the overall risk of HCC recurrence post-transplantation.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Informed Consent

Not applicable. Waiver of consent was granted by the IRB as this was a retrospective study.

Author Contributions

Dr. Kelly M. Zucker: study concept and design, analysis and interpretation of data, drafting of manuscript. Dr. Paul A. Gomez: study concept and design, analysis and interpretation of data. Olivia Kezirian: statistical analysis. Dr. Shivang Mehta: study concept and design, analysis and interpretation of data, drafting of manuscript, study supervision.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

HCC: hepatocellular carcinoma; LT: liver transplantation; AFP: alpha fetoprotein; BMI: body mass index; LRT: locoregional therapies; HAS: hepatic artery stenosis; HAT: hepatic artery thrombosis; DVT: deep venous thrombosis

References

1. Agopian VG, Harlander-Locke M, Zarrinpar A, Kaldas FM, Farmer DG, Yersiz H, Finn RS, et al. A novel prognostic nomogram accurately predicts hepatocellular carcinoma recurrence after liver transplantation: analysis of 865 consecutive liver transplant recipients. J Am Coll Surg. 2015;220(4):416-427.
2. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, Camerini T, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol. 2009;10(1):35-43.
3. Au KP, Chok KSH. Multidisciplinary approach for post-liver transplant recurrence of hepatocellular carcinoma: A proposed management algorithm. World J Gastroenterol. 2018;24(45):5081-5094.
4. Valdivieso A, Bustamante J, Gastaca M, Uriarte JG, Ventoso A, Ruiz P, Fernandez JR, et al. Management of hepatocellular carcinoma recurrence after liver transplantation. Transplant Proc. 2010;42(2):660-662.
5. Tabrizian P, Jibara G, Shrager B, Schwartz M, Roayaie S. Recurrence of hepatocellular cancer after resection: patterns, treatments, and prognosis. Ann Surg. 2015;261(5):947-955.
6. Mehta N, Heimbach J, Lee D, Dodge JL, Harnois D, Burns J, Sanchez W, et al. Wait time of less than 6 and greater than 18 months predicts hepatocellular carcinoma recurrence after liver transplantation: proposing a wait time "Sweet Spot". Transplantation. 2017;101(9):2071-2078.
7. Willems M, Sterneck M, Langer F, Jung R, Haddad M, Hagel C, Kuetemeier R, et al. Recurrent deep-vein thrombosis based on homozygous factor V Leiden mutation acquired after liver transplantation. Liver Transpl. 2003;9(8):870-873.
8. Yip J, Bruno DA, Burmeister C, Kazimi M, Yoshida A, Abouljoud MS, Schnickel GT. Deep vein thrombosis and pulmonary embolism in liver transplant patients: risks and prevention. Transplant Direct. 2016;2(4):e68.