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

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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

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,
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).

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 ± 706.0 | 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.

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
and 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.

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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.

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.
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