Research Article

Achieving Complete Remission of Hepatocellular Carcinoma: A Significant Predictor for Recurrence-Free Survival after Liver Transplantation

Christin Bürger 1, Miriam Maschmeier 1, Anna Hüsing-Kabar 1, Christian Wilms 1, Michael Köhler 2, Martina Schmidt 1, Hartmut H. Schmidt 1, and Iyad Kabar 1

1Department of Medicine B for Gastroenterology and Hepatology, University Hospital Muenster, 48149 Muenster, Germany
2Department of Clinical Radiology, University Hospital Muenster, 48149 Muenster, Germany

Correspondence should be addressed to Christin Bürger; christin.buerger@ukmuenster.de

Received 24 July 2018; Accepted 1 January 2019; Published 8 January 2019

Academic Editor: Maikel P. Peppelenbosch

Copyright © 2019 Christin Bürger et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Background. Liver transplantation (LT) is a curative treatment for hepatocellular carcinoma (HCC) and the underlying primary liver disease; however, tumor recurrence is still a major issue. Therefore, the aim of this study was to assess predictors and risk factors for HCC recurrence after LT in patients within and outside the Milan criteria with a special focus on the impact of different bridging strategies.

Methods. All patients who underwent LT for HCC between 07/2002 and 09/2016 at the University Hospital of Muenster were consecutively included in this retrospective study. Database research was performed and a multivariable regression analysis was conducted to explore potential risk factors for HCC recurrence. Results. A total of 82 patients were eligible for the statistical analysis. Independent of bridging strategy, achieving complete remission (CR) was significantly associated with a lower risk for tumor recurrence ($p = 0.029; OR = 0.426, 95\% CI 0.198-0.918$). A maximal diameter of lesion < 3 cm was also associated with lower recurrence rates ($p = 0.040; OR = 0.140, 95\% CI 0.022-0.914$). Vascular invasion proved to be an independent risk factor for HCC recurrence ($p = 0.004; OR = 11.357, 95\% CI 2.142-60.199$). Conclusion. Achieving CR prior to LT results in a significant risk reduction of HCC recurrence after LT independent of the treatment modalities applied.

1. Introduction

Despite increasing approvals of novel antiviral drugs against hepatitis B and C, the incidence of hepatocellular carcinoma (HCC), the most common primary liver tumor, is still rising worldwide. Globally, it constitutes the 2nd leading cause of cancer-related death [1–5]. Most HCC develop in a cirrhotic liver [6]. Alcoholic cirrhosis, active hepatitis B and C, and nonalcoholic fatty liver disease have been identified as the main underlying diseases. Prevalence is higher in males than in females. A more frequent exposition to risk factors is assumed to be one cause of this male predominance [7]. HCC is an often lethal disease with a combined 5-year survival rate of only about 15% in the USA and about 12% in Europe [8]. Liver transplantation (LT) is the favored treatment for patients with HCC and cirrhosis, as it can cure both the tumor with all intrahepatic foci and the underlying cirrhosis [5, 7]. HCC makes up about 20% of all indications for LT in Europe [8]. Waiting time for a deceased donor liver can be long due to shortage of cadaveric organs for transplantation. In many cases bridging strategies including surgery, loco-regional, molecular targeted, and radio-oncological procedures are applied aiming at prevention of tumor progression and subsequently gaining time to LT [9–12]. For patients with an advanced tumor stage, the same interventions are performed aiming at downstaging and thus making LT possible in the first place [13].

HCC recurrence is one significant problem after LT with recurrence rates of approximately 15-20%. Due to limited treatment options, prognosis of such recurrence is still poor with a median survival of less than 12 months after diagnosis [14]. Multiple possible risk factors have been investigated in order to optimize patient selection for transplant listing and to lower the risk of tumor recurrence post LT, but associated
risk factors are still not completely evaluated. The Milan criteria (single lesion ≤ 5 cm or a maximum of three lesions ≤ 3 cm) are widely used as a decision basis for patient selection for LT, especially as HCC recurrence rates dropped significantly after application since 1996 [15]. However, using the Milan criteria as the only basis to select transplant candidates may result in excluding HCC patients who may still profit from LT. Several studies suggest alternatives, such as the University of California San Francisco (UCSF) criteria (single lesion <6.5 cm, maximum of three lesions with none >4.5 cm, and cumulative tumor size <8 cm) which render similar recurrence-free survival rates [16]. Biological features of the tumor (grading, microvascular or lymphatic invasion, alpha fetoprotein (AFP) level, and response to bridging therapies) also play an important role regarding HCC recurrence rates [17]. However, some of these features such as microvascular or lymphatic invasion cannot be assessed prior to LT. Tumor grading may be retrieved by liver biopsy, but there are some data indicating a higher risk of HCC recurrence by spreading tumor cells in the biopsy channel [18]. Posttransplant studies indicate that the immunosuppressive regimen may have an impact on tumor recurrence. Calcineurin inhibitors (CNI), the most widely used immunosuppressive medication, have been associated with increased tumor growth and a higher risk of tumor recurrence [19, 20]. Mammalian targets of rapamycin (mTOR)-inhibitors (Sirolimus, Everolimus) have antiproliferative and antiangiogenic properties and some data indicate a protective role [21].

In the present study, we analyzed recipient- and donor-related predictors and risk factors for HCC recurrence after LT with a special focus on the role of different bridging modalities.

2. Materials and Methods

We conducted a single-center, retrospective study on patients who were treated for HCC and underwent LT between 07/2002 and 09/2016 at the University Hospital of Muenster and who received follow-up care at this center. Inclusion criteria were age over 18 years, HCC as the main indication for LT, available recipient, and donor data. All transplanted organs were retrieved from deceased donors and implanted in orthotopic technique. Extrahepatic tumor manifestations were ruled out immediately before transplantation by chest and abdominal CT-scan and/or MRI. HCC recurrence was defined as any confirmed intra- or extrahepatic HCC lesion detected by radiographic or histopathological diagnostics after LT. Standard posttransplant follow-up included abdominal multislice-imaging (CT- or MRI scans) every 6 months and alpha-fetoprotein measurements as well as abdominal sonography in 3-monthly intervals; further diagnostics were conducted symptom oriented. Patient data were extracted from health care files at the University Hospital of Muenster. Approval to the study was given by the local ethical committee and it was conducted in conformity to the 1975 Declaration of Helsinki (7th Revision of October 2013).

Demographic data collected for both recipients and donors were age, sex, and BMI. Further patient related demographic values were waiting time from HCC diagnosis to LT and survival time after LT. Furthermore, we evaluated the underlying hepatic diseases. Tumor related data and histopathological properties were gained from pre-LT radiological diagnostics and histopathological findings of pre-LT biopsy samples and the liver explants. Reported were maximum tumor size, the number of nodules, fulfillment of the Milan criteria, tumor grading (according to the Edmondson and Steiner grading system) [22], microvascular and lymphatic invasion, and the stage of liver fibrosis (according to the fibrosis score according to Batts and Ludwig) [23]. Clinical response to bridging therapies was subdivided into no detectable remission, partial or complete remission (CR) according to the level of tumor necrosis in the histopathological exam of the explant liver. The definition of CR was the absence of vital tumor in the explant liver. Partial remission was defined as presence of partial tumor necrosis but persisting vital tumor residues. Evaluated pre-LT bridging and downstaging treatments were transarterial chemoembolization (TACE), Sorafenib, surgical resection, selective internal radiation therapy (SIRT), or other radiation treatment and radiofrequency ablation (RFA). We also included the highest pre-LT AFP level, CRP-level directly before LT, and sampling of a pre-LT targeted biopsy of the tumor in this study.

2.1. Immunosuppression after LT. Post-LT immunosuppressive regimen was documented. All patients received an intraoperative induction therapy with 500 mg of prednisolone. After LT, most patients received an immunosuppressive combination therapy. Maintenance immunosuppression comprised various combinations of the following three drugs: Tacrolimus and/or Everolimus and/or Mycophenolate Mofetil.

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 24 (SPSS Inc., Chicago, Illinois).

3. Results

A total of 82 patients were eligible for the statistical analysis. The majority of LT recipients were male (82.9%) and mean age at LT was 57.2 ± 9.4. Mean donor age was 50.9 ± 15.4 years. The most common underlying liver diseases were alcoholic cirrhosis and viral hepatitis (B and C) in 25.6% and 51.2%, subsequently. The majority of patients had either liver cirrhosis (89%) or an advanced stage of liver fibrosis (4.9%, grade 3 according to Batts and Ludwig score) [23]. A targeted liver biopsy was obtained in 52 subjects (65.0%). Tumor grading ranged between well- and undifferentiated; 64.6% showed moderate differentiation (grade 2 according to the Edmondson and Steiner grading system) [22]. More than half of the included patients (53.7%) were outside the Milan criteria at time of HCC diagnosis. Median waiting time from HCC diagnosis until LT was 7 (IQR 2-12) months. 64 subjects received bridging treatment prior to LT. The majority of them underwent TACE (45, 54.9%). Remission could be reached in 59 subjects (71.9%). Of them, 43 (52.4%) achieved partial and 16 (19.5%) CR. Tumor recurrence after LT occurred in a total of 28 subjects (34.1%), and median recurrence-free survival time was 12.50 (IQR 6-28,25) months. A total of 36 patients
died during the observed time period; 23 of them suffered from tumor recurrence. Median survival time of all patients after LT was 49.50 (IQR 24.50-84.75) months. Predictors for achieving a CR were the presence of only one tumor lesion (p=0.001; OR 10.7, 95% CI 2.7-42.0) and/or the fulfilment of the Milan criteria (p = 0.004; OR 7.1, 95% CI 1.8-27.4). AFP level (p=0.68) and the grade of liver fibrosis (p=0.37) were not statistically significant factors regarding achievement of CR. Further demographic and clinical data are depicted in Table 1.

Multivariable regression analysis revealed CR (p = 0.029; OR = 0.426, 95% CI 0.198-0.914) to be statistically significant for HCC recurrence. Detailed results of univariable and multivariable analysis are included in Table 2.

Kaplan-Meier curves in Figure 1 demonstrate the recurrence-free survival probability with regard to the different risk factors.

4. Discussion

HCC recurrence is a major issue after LT. Treatment options are limited and in the majority of cases, only palliative
Table 1: Characteristics of recipients, tumors, and donors.

| Number of subjects | 82 |
|--------------------|----|
| **Characteristics of recipients** | | |
| Age at LT [years] | 57.2 ± 9.4 |
| Males | 68 (82.9 %) |
| Body Mass Index [kg/m²] | 27.56 ± 5.07 |
| **Primary liver disease** | | |
| Alcoholic cirrhosis | 21 (25.6 %) |
| Autoimmune hepatitis | 2 (2.4 %) |
| Hepatitis B | 21 (25.6%) |
| Hepatitis C | 21 (25.6%) |
| Non-alcoholic fatty liver disease | 3 (3.7 %) |
| Hemochromatosis | 2 (2.4 %) |
| Cryptogenic cirrhosis | 8 (9.8 %) |
| Secondary sclerosing cholangitis | 1 (1.2 %) |
| Alpha-1-deficiency | 1 (1.2 %) |
| Drug-induced liver injury | 2 (2.4 %) |
| **Fibrosis (according to Batts and Ludwig score)** | | |
| none | 5 (6.1%) |
| grade 3 | 4 (4.9%) |
| grade 4 | 73 (89.0 %) |
| **Time from HCC diagnosis to LT [months]** | 7 (IQR 2-12) |
| **Immunosuppression** | | |
| Ciclosporin | 10 (12.2 %) |
| Tacrolimus | 56 (68.3%) |
| Everolimus | 23 (28.0 %) |
| Sirolimus | 14 (17.1 %) |
| Mycophenolate Mofetil | 62 (75.6 %) |
| **Survival after LT [months] (all patients)** | 49.50 (IQR 24.50-84.75) |
| male patients | 42.00 (IQR 23.50-91.50) |
| female patients | 59.50 (IQR 27.50-74.25) |
| **Death** | 36 (43.9 %) |
| **Recurrence** | 28 (34.1 %) |
| **Recurrence-free survival [months]** | 12.50 (IQR 6-28.25) |
| **Therapy for HCC (bridging/downstaging) before LT** | | |
| No therapy | 17 (20.7%) |
| TACE | 45 (54.9 %) |
| SIRT/radiation | 8 (9.8%) |
| Resection | 16 (19.5%) |
| Radiofrequency ablation | 8 (9.8%) |
| **Remission** | | |
| partial | 43 (52.4 %) |
| complete | 16 (19.5 %) |
| **Targeted biopsy before LT** | 52 (65.0 %) |
| **Tumor characteristics** | | |
| AFP pre-LT [ng/ml] | 13850 (IQR 3350-135973) |
| Milan Criteria fulfilled | 38 (46.3 %) |
| Number of HCC lesions: | | |
| 1 | 32 (39.0 %) |
| 2-3 | 25 (30.5 %) |
| > 3 | 9 (11.0 %) |
| Disseminated tumor infiltration | 16 (19.5 %) |
| Maximum size of HCC lesion(s) [cm] | | |
| < 3 | 30 (36.6 %) |
| 3-5 | 25 (30.5 %) |
| >5 | 26 (31.7 %) |
| Microvascular invasion | 21 (25.6 %) |
| Lymphatic invasion | 5 (6.1 %) |
| Tumor Grading | | |
| Complete remission and no biopsy prior to LT | 6 (7.3 %) |
| grade 1 | 12 (14.6 %) |
| grade 2 | 53 (64.6 %) |
| grade 3 | 9 (11.0 %) |
| grade 4 | 2 (2.4 %) |
therapeutic measures are available [14, 24]. Further evaluation of risk factors and protective properties regarding tumor recurrence is necessary for assessing the hazard of each patient as well as in helping the treating physicians in developing new strategies to reduce HCC recurrence after LT. This is especially crucial in times of organ shortage.

The presence of only one lesion was the strongest predictor for achievement of CR prior to LT in our study, independent of its size. This finding supports data that aim to extend the selection criteria for transplant candidates such as the study by Yao et al. introducing the UCSF Criteria [16].

In our study, achieving CR prior to LT was significantly associated with reduced recurrence rates of HCC. This fact may be due to a less aggressive biological tumor behavior as discussed before [25–27]. Our data confirm the results of a former large scale study from the US Multicenter HCC Transplant Consortium (UMHTC) on patients inside the Milan criteria, which showed that achieving CR is crucial, leading to better outcomes in recurrence-free and overall survival [28]. However, our data suggest that achieving CR significantly reduces HCC recurrence rates after LT irrespective of whether patients were inside or outside the Milan criteria. Of these, 31.7% had tumors larger than 5 cm in diameter.

One further major risk factor for HCC recurrence after LT in our study was vascular invasion. Whereas macrovascular invasion can be detected in preoperative diagnostics in most cases, microvascular invasion is regularly a postoperative finding. So far, no specific preoperative markers or radiological imaging techniques could be established to securely detect microvascular invasion in advance [30, 31]. Preoperative biopsy cannot always render conclusive results due to tumor heterogeneity leading to sampling errors [32, 33]. Generally, vascular invasion may indicate a systemic character of the HCC [34].

Another independent risk factor for HCC recurrence after LT in our study was vascular invasion. Whereas macrovascular invasion can be detected in preoperative diagnostics in most cases, microvascular invasion is regularly a postoperative finding. So far, no specific preoperative markers or radiological imaging techniques could be established to securely detect microvascular invasion in advance [30, 31]. Preoperative biopsy cannot always render conclusive results due to tumor heterogeneity leading to sampling errors [32, 33]. Generally, vascular invasion may indicate a systemic character of the HCC [34].

One further major risk factor for HCC recurrence after LT in our study was vascular invasion. Whereas macrovascular invasion can be detected in preoperative diagnostics in most cases, microvascular invasion is regularly a postoperative finding. So far, no specific preoperative markers or radiological imaging techniques could be established to securely detect microvascular invasion in advance [30, 31]. Preoperative biopsy cannot always render conclusive results due to tumor heterogeneity leading to sampling errors [32, 33]. Generally, vascular invasion may indicate a systemic character of the HCC [34].
analysis only. However, multivariable analysis showed no association between number of HCC lesions and HCC recurrence. This fact may be due to the extensive use of several bridging strategies at our center in order to achieve CR in each case irrespective of lesions number and tumor spread within the liver. These findings are partially consistent with studies that showed a favorable prognostic impact of the Milan criteria and lead to establish these for patient selection priority for LT [15]. However, our data indicate that patient selection for LT solely dependent on the Milan criteria seems to be too strict and may exclude patients that still greatly benefit from LT, especially as these criteria may discharge tumor biology and further significant prognostic factors such as tumor response to treatments prior to LT [16, 35–39].

Remarkably, in our study, performing targeted tumor biopsy before LT was not associated with increased HCC recurrence rates. This fact may debunk former results [18, 40, 41]. Therefore, performing a biopsy in HCC, especially in case of unclear liver masses as well as in cases with inconsistent contrast enhanced imaging, seems to be safe and even reasonable.

Time on the waiting list was not predictive for a higher risk for HCC recurrence in our study. This finding may be due to the fact that the majority of patients received bridging therapies and further underlines the major role of tumor biology on tumor progression [12, 42].

Data on recurrence protection using mTOR inhibitors is still controversial. Most study populations were small and until now, only few randomized controlled trials and prospective studies are available [21, 43, 44]. In our study, univariate analysis showed a strong tendency towards a significant reduction of HCC recurrence ($p = 0.053$) in patients who received an Everolimus based immunosuppression. However multivariable analysis showed no influence of Everolimus on HCC recurrence. Sirolimus based regimens were rare in our study collective and were thus not included in the statistical analysis. Nevertheless, as long as no clear statement can be made, an mTOR based immunosuppressive regimen may be considered in patients after LT for HCC without contraindications.

5. Conclusions

The main goal of treatment in HCC patients waiting for LT should be reaching CR as this achievement is crucial in reducing HCC recurrence rates after LT. The applied strategy, number, and combination of treatments were according to our data insignificant. Therefore, selection of treatment modalities should primarily be adjusted in accordance with both patient characteristics such as liver function and tumor properties such as diameter and extension. Microvascular invasion is another major risk factor for HCC recurrence that surely has prognostic relevance. However, this risk factor cannot be modified prior to LT.

Data Availability

Data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

We would like to thank Bryan G. Miller for language editing.

References

[1] J. Ferlay, I. Soerjomataram, M. Ervik et al., “GLOBOCAN 2012 v1.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11,” in Proceedings of the, International Agency for Research on Cancer, 2012, http://globocan.iarc.fr.

[2] J. Ferlay, I. Soerjomataram, R. Dikshit et al., “Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN,” International Journal of Cancer, vol. 136, no. 5, pp. E359–E386, 2015.

[3] F. Bray, J.-S. Ren, E. Masuyer, and J. Ferlay, “Global estimates of cancer prevalence for 27 sites in the adult population in 2008,” International Journal of Cancer, vol. 132, no. 5, pp. 1133–1145, 2013.

[4] J. L. Petrick, M. Braunlin, M. Laversanne, P. C. Valery, E. Bray, and K. A. McGlynn, “International trends in liver cancer incidence, overall and by histologic subtype, 1978–2007,” International Journal of Cancer, vol. 139, no. 7, pp. 1534–1545, 2016.

[5] J. M. Llovet, A. Burroughs, and J. Bruix, “Hepatocellular carcinoma,” Lancet, vol. 362, no. 9399, pp. 1907–1917, 2003.

[6] A. Cucchetti, M. Cescon, E. Bigonzi et al., “Priority of candidates with hepatocellular carcinoma awaiting liver transplantation: Time for controlled trials?” Liver Transplantation, vol. 17, no. 11, pp. 1344–1354, 2011.

[7] F. Y. Yao, N. Mehta, J. Flemming et al., “Downstaging of hepatocellular carcinoma before liver transplant: Long-term outcome compared to tumors within Milan criteria,” Hepatology, vol. 61, no. 6, pp. 1968–1977, 2015.

[8] M.-W. Welker, W.-O. Bechstein, S. Zeuzem, and J. Trojan, “Recent hepatocellular carcinoma after liver transplantation—an emerging clinical challenge,” Transplant International, vol. 26, no. 2, pp. 109–118, 2013.
V. Mazzaferro, E. Regalia, R. Doci et al., “Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis,” The New England Journal of Medicine, vol. 334, no. 11, pp. 693–699, 1996.

F. Y. Yao, L. Ferrell, N. M. Bass et al., “Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival,” Hepatology, vol. 33, no. 6, pp. 1394–1403, 2001.

G. C. Sotiropoulos, E. P. Molmenti, C. Lüsch, S. Beckebaum, C. E. Broelsch, and H. Lang, “Meta-analysis of tumor recurrence after liver transplantation for hepatocellular carcinoma based on 1,198 cases,” European Journal of Medical Research, vol. 12, no. 10, pp. 527–534, 2007.

M. A. Silva, B. Hegab, C. Hyde, B. Guo, J. A. C. Buckels, and D. F. Mirza, “Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: A systematic review and meta-analysis,” Gut, vol. 57, no. 11, pp. 1592–1596, 2008.

M. Vivarelli, A. Cucchetti, G. L. Barba et al., “Liver transplantation for hepatocellular carcinoma under calcineurin inhibitors: reassessment of risk factors for tumor recurrence,” Annals of Surgery, vol. 248, no. 5, pp. 857–862, 2008.

S. E. Khorsandi and N. Heaton, “Optimization of immunosuppressive medication upon liver transplantation against HCC recurrence,” Translational Gastroenterology and Hepatology, vol. 1, p. 25, 2016.

A. O. Ferreiro, M. A. Vazquez-Millán, F. S. López, M. G. Gutiérrez, S. P. Díaz, and M. J. L. Patiño, “Everolimus-based immunosuppression in patients with hepatocellular carcinoma at high risk of recurrence after liver transplantation: a case series,” Transplantation Proceedings, vol. 46, no. 10, pp. 3496–3501, 2014.

H. A. Edmondson and P. E. Steiner, “Primary carcinoma of the liver: a study of 100 cases among 48,900,” Cancer, vol. 7, no. 3, pp. 462–503, 1954.

K. P. Batts and J. Ludwig, “Chronic hepatitis: an update on terminology and reporting,” The American Journal of Surgical Pathology, vol. 19, no. 12, pp. 1409–1417, 1995.

N. DeAngelis, F. Landi, M. C. Carra, and D. Azoulay, “Management of recurrent hepatocellular carcinoma after liver transplantation: A systematic review,” World Journal of Gastroenterology, vol. 21, no. 39, pp. 11185–11198, 2015.

G. Otto, S. Herber, M. Heise et al., “Response to transarterial chemoembolization as a biological selection criterion for liver transplantation in hepatocellular carcinoma,” Liver Transplantation, vol. 12, no. 8, pp. 1260–1267, 2006.

F. Y. Yao, R. K. Kerlan Jr., R. Hirose et al., “Excellent outcome following down-staging of hepatocellular carcinoma prior to liver transplantation: an intention-to-treat analysis,” Hepatology, vol. 48, no. 3, pp. 819–827, 2008.

A. Viveiros, H. Zoller, and A. Finkerstedt, “Hepatocellular carcinoma: When is liver transplantation oncologically futile?” Translational Gastroenterology and Hepatology, vol. 2, p. 36, 2017.

V. G. Agopian, M. P. Harlander-Locke, R. M. Ruiz et al., “Impact of Pretransplant Bridging Locoregional Therapy for Patients With Hepatocellular Carcinoma Within Milan Criteria Undergoing Liver Transplantation,” Annals of Surgery, vol. 266, no. 3, pp. 525–535, 2017.

H. W. Lee and K.-S. Suh, “Liver transplantation for advanced hepatocellular carcinoma,” Clinical and Molecular Hepatology, vol. 22, no. 3, pp. 309–318, 2016.

M. Rodriguez-Perálvrez, T. V. Luong, L. Andreana, T. Meyer, A. P. Dhillon, and A. K. Burroughs, “A Systematic Review of Microvascular Invasion in Hepatocellular Carcinoma: Diagnostic and Prognostic Variability,” Annals of Surgical Oncology, vol. 20, no. 1, pp. 325–339, 2013.

K. Shirabe, T. Toshima, K. Kimura et al., “New scoring system for prediction of microvascular invasion in patients with hepatocellular carcinoma,” Liver International, vol. 34, no. 6, pp. 937–941, 2014.

L. Wang, J. Wang, X. Zhang et al., “Diagnostic Value of Preoperative Needle Biopsy for Tumor Grading Assessment in Hepatocellular Carcinoma,” PLoS ONE, vol. 10, no. 12, p. e0144216, 2015.

F. An, M. Matsuda, H. Fujii et al., “Tumor heterogeneity in small hepatocellular carcinoma: Analysis of tumor cell proliferation, expression and mutation of p53 and β-catenin,” International Journal of Cancer, vol. 93, no. 4, pp. 468–474, 2001.

Y. K. Park, S. K. Song, B. Kim, S. Park, C. Chung, and H. Wang, “Prognostic significance of microvascular invasion in tumor stage for hepatocellular carcinoma,” World Journal of Surgical Oncology, vol. 15, no. 1, p. 87, 2017.

V. Mazzaferro, C. Sposito, J. Zhou et al., “Metroxicet 2.0 Model for Analysis of Competing Risks of Death After Liver Transplantation for Hepatocellular Carcinoma,” Gastroenterology, vol. 154, no. 1, pp. 128–139, 2018.

A. Kornberg, “Liver Transplantation for Hepatocellular Carcinoma beyond Milan Criteria: Multidisciplinary Approach to Improve Outcome,” ISRN Hepatology, vol. 2014, Article ID 706945, 25 pages, 2014.

E. C. de Ataide, M. Garcia, T. J. Mattosinho, J. R. Almeida, C. A. Escanhoela, and I. F. Boin, “Predicting survival after liver transplantation using up-to-seven criteria in patients with hepatocellular carcinoma,” Transplantation Proceedings, vol. 44, no. 8, pp. 2438–2440, 2012.

X. Xu, D. Lu, Q. Ling et al., “Liver transplantation for hepatocellular carcinoma beyond the Milan criteria,” Gut, vol. 65, no. 6, pp. 1035–1041, 2016.

V. Mazzaferro, M. L. Llovet, R. Miceli et al., “Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis,” The Lancet Oncology, vol. 10, no. 1, pp. 35–43, 2009.

R. Stigliano, L. Marelli, D. Yu, N. Davies, D. Patch, and A. K. Burroughs, “Seeding following percutaneous diagnostic and therapeutic approaches for hepatocellular carcinoma. What is the risk and the outcome? seeding risk for percutaneous approach of HCC,” Cancer Treatment Reviews, vol. 33, no. 5, pp. 437–447, 2007.

D. Seehofer, R. Öllinger, T. Denecke et al., “Blood Transfusions and Tumor Biopsy May Increase HCC Recurrence Rates after Liver Transplantation,” Journal of Transplantation, vol. 2017, Article ID 9731095, 9 pages, 2017.

A. Finkerstedt, A. Vikoler, M. Portenkirchner et al., “Excellent post-transplant survival in patients with intermediate stage hepatocellular carcinoma responding to neoadjuvant therapy,” Liver International, vol. 36, no. 5, pp. 688–695, 2016.

E. K. Geissler, A. A. Schnitzbauer, C. Zülke et al., “Sirolimus Use in Liver Transplant Recipients With Hepatocellular Carcinoma,” Transplantation, vol. 100, no. 1, pp. 116–125, 2016.

E. Cholongitas, C. Mamou, K. I. Rodríguez-Castro, and P. Burra, “Mammalian target of rapamycin inhibitors are associated with lower rates of hepatocellular carcinoma recurrence after liver transplantation: a systematic review,” Transplant International, vol. 27, no. 10, pp. 1039–1049, 2014.