RESEARCH ARTICLE

AFP ratio predicts HCC recurrence after liver transplantation

Christine Koch[1]*, **Theresa Bette**[1], **Oliver Waidmann**[1], **Natalie Filmann**[2], **Christopher Schrecker**[1], **Jörg Trojan**[1], **Nina Weiler**[1], **Johannes Vermehren**[1], **Andreas A. Schnitzbauer**[3], **Wolf Otto Bechstein**[3], **Stefan Zeuzem**[1], **Eva Herrmann**[2], **Martin-Walter Welker**[1]

1 Medizinische Klinik 1, Universitätsklinikum Frankfurt, Frankfurt, Germany, **2** Institut für Biostatistik und Mathematische Modellierung, Universitätsklinikum Frankfurt, Frankfurt, Germany, **3** Klinik für Allgemein- und Viszeralchirurgie, Universitätsklinikum Frankfurt, Frankfurt, Germany

* christine.koch@kgu.de

Abstract

Background/aims

Hepatocellular carcinoma (HCC) is a leading indication for liver transplantation (LT) world-wide. Early identification of patients at risk for HCC recurrence is of paramount importance since early treatment of recurrent HCC after LT may be associated with increased survival. We evaluated incidence of and predictors for HCC recurrence, with a focus on the course of AFP levels.

Methods

We performed a retrospective, single-center study of 99 HCC patients who underwent LT between January 28th, 1997 and May 11th, 2016. A multi-stage proportional hazards model with three stages was used to evaluate potential predictive markers, both by univariate and multivariable analysis, for influences on 1) recurrence after transplantation, 2) mortality without HCC recurrence, and 3) mortality after recurrence.

Results

19/99 HCC patients showed recurrence after LT. Waiting time was not associated with overall HCC recurrence (HR = 1, p = 0.979). Similarly, waiting time did not affect mortality in LT recipients both with (HR = 0.97, p = 0.282) or without (HR = 0.99, p = 0.685) HCC recurrence. Log_{10}-transformed AFP values at the time of LT (HR 1.75, p = 0.023) as well as after LT (HR 2.07, p = 0.037) were significantly associated with recurrence. Median survival in patients with a ratio (AFP at recurrence divided by AFP 3 months before recurrence) of 0.5 was greater than 70 months, as compared to a median of only 8 months in patients with a ratio of 5.

Conclusion

A rise in AFP levels rather than an absolute threshold could help to identify patients at short-term risk for HCC recurrence post LT, which may allow intensification of the surveillance strategy on an individualized basis.

Introduction

Hepatocellular carcinoma (HCC) is a leading indication for liver transplantation (LT) in East Asia, Europe, and North America [1–3]. The overall five-year survival rate of patients with HCC is comparable to non-malignancy indications, when tumor size is limited at the time of LT [4,5]. The Milan criteria are commonly used to decide whether patients with HCC are eligible for LT or not, and are defined as a single HCC nodule not exceeding 5 cm, or a maximum of three nodules not exceeding 3 cm each [5]. While some studies have investigated whether transplantation beyond the Milan criteria is feasible [6–8], HCC recurrence after LT is still a major concern even when the Milan criteria are fulfilled [9]. Despite general efforts and advances in the treatment of HCC in recent years [10], treatment of recurrent HCC after LT remains a challenge due to the lack of prospective, controlled studies addressing this issue [11]. Hence, early identification of patients at risk for HCC recurrence is of paramount importance.

Currently, there is no clear guideline for follow-up and surveillance of patients after LT for HCC [12]. It would be desirable to predict the individual risk for HCC recurrence more accurately, thereby reducing the need for repeated radiation exposure and the use of contrast agents. In recent years, a number of donor-related and transplant-related risk factors for tumor development besides immunosuppression have been described, to facilitate identification of patients at risk for an early recurrence [13–15]. Alpha-fetoprotein (AFP) is an established and routine tumor marker in patients with HCC, which is readily available for patients who were AFP-positive before LT. Of note, AFP values >1000 ng/ml before LT have been associated with the risk of HCC recurrence after LT [16–18]. High AFP serum levels may be a surrogate parameter for vascular infiltration, a well-characterized predictor for HCC recurrence after LT [19]. However, the clinical value of AFP in HCC surveillance after LT has not been closely investigated.

In the current study, we evaluated the incidence of and predictors for HCC recurrence (with a focus on the course of AFP levels) in liver graft recipients, who suffered from HCC prior to LT and were transplanted within the Milan criteria, in a high MELD region with correspondingly longer waiting times.

Methods

Study design

The aim of this retrospective, single-center study was to investigate the recurrence rate of HCC after LT at a German liver transplant center and to analyze predictors for HCC recurrence. Patients transplanted elsewhere were included if they participated in our clinic's liver post-transplant surveillance program and if sufficient data were available. The study was approved by the institutional review board (internal reference number 268/13-006) of the University Hospital Frankfurt. Informed consent to participate in the local liver transplant registry was obtained from all patients alive at the time of the study. In accordance with legal

requirements and ethics committee vote, data of deceased patients were also included in the analysis. Inclusion criteria of the registry were a history of liver transplantation for any indication and age older than 18 years. Patients with HCC before liver transplantation were identified from the registry and the respective data sets were transferred to a separate database, which was the basis for further analyses as reported here. Finally, all data were pseudonymized for analysis and only non-identifiable data were published. Data from individual patients may have been reported previously with respect to different topics [20–22].

Patient data

The study database was based on local electronic health records including epidemiological data, age, body mass index (BMI), overall and recurrence-free survival with regard to HCC after LT and, if applicable, dates of death. Diagnosis of HCC recurrence after LT was confirmed by radiographic and/or histopathologic examination. Laboratory data analyzed included AFP serum values, as well as virological parameters including hepatitis B/C and CMV status. Finally, a medication history including details of immunosuppression and a full medical history were obtained. Data closure and end of follow-up was February 11th, 2019.

Statistical analyses

Clinical and biochemical patient characteristics were expressed as mean ± standard deviation (SD) or median and range, as appropriate. A multi-stage proportional hazards model with three stages was used to evaluate potential predictive markers, both by univariate and multi-variable analysis, for influences on 1) recurrence after transplantation, 2) mortality without HCC recurrence, and 3) mortality after recurrence. Endpoints of the regression analysis were recurrence and death, and these were analyzed as strata in the multi-stage model. HCC recurrence was analyzed as a factor with proportional influence on death and was also included in the otherwise univariate analysis of the multi-stage model. When analyzing AFP as a predictor for recurrence and mortality, only values transformed to $\log_{10}(1+AFP)$ were included in the regression model. Furthermore, the normal range of AFP kinetics in patients without recurrence was described by empirical 90% quantiles. Software: R with the packages "survival" and "mstate" (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics and incidence of HCC recurrence

A total of 99 patients who underwent LT for HCC between January 28th, 1997 and May 11th, 2016 were included in the current study. Of these 99 patients, 22 were transplanted between 1997 and 2006. 19/99 patients suffered an HCC recurrence in the observation period. Detailed patient characteristics are shown in Table 1. The mean waiting time between HCC diagnosis and transplantation was 12.0 ± 9.3 months (median 12.0 months, IQR 5.5–15.5). Waiting time was not associated with overall HCC recurrence (HR = 1, p = 0.979). Similarly, waiting time did not affect mortality in LT recipients both with (HR = 0.97, p = 0.282) or without (HR = 0.99, p = 0.685) HCC recurrence.

Clinical predictors associated with HCC recurrence and mortality with and without HCC recurrence

A thorough overview of the risk analysis for HCC recurrence is given in Table 1. In detail, larger tumor size (T2 vs. T0, HR = 8.53, p = 0.043; T3 vs. T0, HR 30.5, p = 0.001), vascular infiltration (HR = 11.39, p<0.001), and higher AFP values ($\log_{10}$-transformed; HR = 2.25 for a

Table 1. Patient baseline characteristics (at LT).

	all patients (n = 99)	influence on recurrence		influence on mortality without recurrence		influence on mortality after recurrence	
		HR1	p-value	HR2	p-value	HR3	p-value
female gender, n (%)	31/99 (31.3%)	0.53	0.256	1.20	0.652	0.66	0.537
age [y], mean (SD)	55.6 (6.7)	1.01	0.774	1.03	0.283	1.05	0.416
median (IQR)	56.0 (52.0–60.0)						
BMI [kg/m^2], mean (SD)	26.6 (5.2)	1.03	0.503	0.99	0.786	1.08	0.156
median (IQR)	26.4 (23.1–29.1)						
etiology of liver disease, n (%)							
viral hepatitis only	65/99 (65.7%)	Ref		Ref		Ref	
Alcohol	17/99 (17.2%)	0.56	0.442	0.74	0.591	3.13	0.178
viral hepatitis and alcohol	7/99 (7.1%)	2.35	0.183	n.a.	n.a.	3.95	0.074
alcohol and other	2/99 (2.0%)	n.a.	n.a.	3.44	.099	n.a.	n.a.
Other	8/99 (8.1%)	0.55	0.565	0.40	0.369	3.44	0.285
waiting time (months), mean (SD)	12.0 (9.3)	1.00	0.979	0.99	0.658	0.97	0.282
median (IQR)	12.0 (5.5–15.5)						
labMeld before LT, mean (SD)	13.5 (6.2)	0.96	0.392	0.99	0.863	1.07	0.094
median (IQR)	12.0 (8.8–15.0)						
SE-Meld before LT, mean (SD)	28.9 (3.4)	0.87	0.076	0.96	0.575	1.16	0.263
median (IQR)	29.0 (28.0–31.0)						
SE criteria at listing, n (%)	52/84 (61.9%)	0.59	0.271	1.32	0.574	0.38	0.060
SE criteria at LT, n (%)	69/86 (80.2%)	0.62	0.366	0.58	0.301	0.59	0.328
Milan criteria at initial diagnosis, n (%)	63/77 (81.8%)	0.33	**0.033**	1.49	0.596	0.44	0.141
Milan criteria at LT, n (%)	75/85 (88.2%)	0.33	0.058	0.65	0.490	0.60	0.397
HBsAg positive, n (%)	7/82 (8.5%)	0.87	0.897	1.09	0.911	n.a.	n.a.
anti-HBc positive, n (%)	44/82 (53.7%)	1.88	0.248	1.74	0.275	1.485	0.562
anti-HIV positive, n (%)	2/58 (3.4%)	9.56	**0.045**	n.a.	n.a.	n.a.	n.a.
anti-CMV positive, n (%)	68/89 (76.4%)	4.22	0.163	0.60	0.261	0.88	0.907
diabetes mellitus, n (%)	34/98 (34.7%)	1.41	0.462	0.90	0.810	0.82	0.687
HbA1c [%], mean (SD)	5.7 (1.2)	1.25	0.449	1.00	0.992	1.48	0.493
median (IQR)	5.4 (4.9–6.4)						
CKD, n (%)	48/99 (48.5%)	0.68	0.415	1.12	0.787	0.72	0.504
AFP [ng/mL], mean (SD)*	1166.7 (7448.6)	2.25	**<0.001**	0.89	0.749	0.85	0.419
median (IQR)	8.2 (4.5–25.7)						
GFR MDRD [ml/min], mean(sd)	84.8 (26.1)	1.00	0.735	1.00	0.692	0.98	0.255
median (IQR)	83.2 (71.2–102.3)						
dialysis, n (%)	2/90 (2.2%)	2.16	0.449	n.a.	n.a.	n.a.	n.a.
grade, n (%)							
G1	19/78 (24.4%)	Ref		Ref		Ref	
G1-2	7/78 (9.0%)	n.a.	n.a.	0.63	0.680	n.a.	n.a.
G2	47/78 (60.3%)	2.93	0.158	1.39	0.573	0.91	0.902
G3	5/78 (6.4%)	49.51	**<0.001**	6.71	0.111	0.61	0.590
T stage, n (%)							
T0	25/96 (26.0%)	Ref		Ref		Ref	
T1	31/96 (32.3%)	n.a.	n.a.	1.04	0.937	n.a.	n.a.
T2	27/96 (28.1%)	8.53	**0.043**	1.71	0.309	n.a.	n.a.
T3	13/96 (13.5%)	30.50	**0.001**	0.57	0.603	n.a.	n.a.
Milan criteria in explanted liver, n (%)	65/94 (69.1%)	0.09	**<0.001**	0.77	0.570	0.24	0.060

(Continued)

Table 1. (Continued)

	all patients (n = 99)	influence on recurrence		influence on mortality without recurrence		influence on mortality after recurrence	
		HR1	p-value	HR2	p-value	HR3	p-value
vascular infiltration, n (%)	11/93 (11.8%)	11.39	**<0.001**	1.60	0.532	1.77	0.255
necrotic tumor, n (%)	12/95 (12.6%)	0.38	0.352	1.06	0.920	n.a.	n.a.

* Log10 transformation for survival analysis

factor of 10, p<0.001) were significantly associated with HCC recurrence. A tumor stage within the Milan criteria markedly reduced the risk of recurrence (HR = 0.09, p<0.001). With regard to overall survival, HCC recurrence was strongly significant (p<0.0001), and was adjusted for in the analysis of the remaining baseline parameters shown in Tables 1 and 2. Here, only transplantation of a split liver graft (with limited case numbers, n = 5, HR = 6.56, p = 0.004) was associated with impaired survival after LT. Multivariate analysis (Table 3) confirmed tumor size (T2/T3), tumor grade (G3), and hospital-based allocation to be associated with risk for recurrence.

AFP for prediction of HCC recurrence

Based on the results of the univariate analysis, we next sought to further investigate the role of AFP as a possible predictive marker for HCC recurrence and mortality as competing endpoints.

In 90% of patients who survived at least 24 months without HCC recurrence, AFP levels were below 46.8 ng/ml at LT, and below 6.27 ng/ml from months 6 through 18 (Fig 1).

We next divided patients who suffered from HCC recurrence after LT in two groups based on AFP levels at LT. The first group consisted of patients with AFP values above 50 ng/ml at LT. Of these, all patients except one had AFP levels above 6.27 ng/ml (90% percentile for non-recurrence from months 6 through 18 after LT) already 3 months before HCC recurrence (Fig 2).

In contrast, only two of the patients with HCC recurrence and AFP levels below 50 ng/ml at LT showed AFP values above the 90% percentile already 3 months before HCC recurrence (Fig 3).

Table 2. Transplant and donor characteristics.

	all patients (n = 99)	influence on recurrence		influence on mortality without recurrence		influence on mortality after recurrence	
		HR1	p-value	HR2	p-value	HR3	p-value
living donor, n (%)	4/98 (4.1%)	1.74	0.593	4.07	0.062	0.98	0.982
split liver graft, n (%)	5/98 (5.1%)	1.67	0.618	6.56	**0.004**	0.98	0.987
female donor, n (%)	41/95 (43.2%)	1.18	0.722	0.59	0.221	0.70	0.484
age donor [y], mean (SD)	54.9 (18.7)	1.01	0.474	0.99	0.432	1.01	0.378
median (IQR)	56.0 (47.0–70.0)						
anti-HBc donor, n (%)	2/13 (15.4%)	n.a.	n.a.	2.65	0.496	n.a.	n.a.
CMV positive donor, n (%)	60/85 (70.6%)	0.85	0.745	1.95	0.290	1.79	0.290
hospital-based allocation, n (%)	3/98 (3.1%)	6.99	**0.012**	3.86	0.197	1.54	0.575
CIT [h], mean (SD)	9.4 (2.8)	0.94	0.483	0.93	0.271	1.07	0.483
median (IQR)	9.8 (8.1–11.2)						

Table 3. multivariate analysis of predictors for HCC recurrence after LT.

	Beta	SE	HR (95% CI)	p-value
T stage T2	2.50	1.07	12.2 (1.50–99.8)	0.0193
T stage T3	3.75	1.07	42.6 (5.15–352.4)	0.0005
Grade G3	2.33	1.73	10.3 (2.48–42.8)	0.0013
hospital-based allocation	-2.28	0.85	0.10 (0.02–0.54)	0.0074

https://doi.org/10.1371/journal.pone.0235576.t003
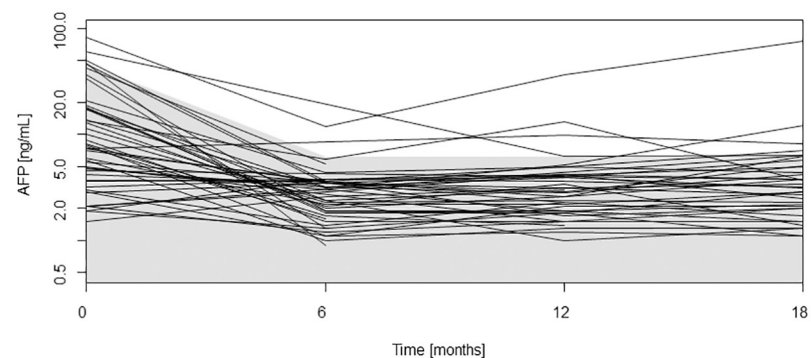

Fig 1. The AFP values within the first 18 months in patients, who survived at least 24 months and who did not develop recurrent HCC in this time period, are given. The shaded area shows the 90% percentile for AFP values (below 46.8 ng/ml at LT and below 6.27 ng/ml from months 6 through 18 after LT).

https://doi.org/10.1371/journal.pone.0235576.g001

Since we found these differences between patients with AFP values above or below 50 ng/ml at the time of LT, we developed a statistical multivariate multi-stage model with AFP as a time-dependent variable. AFP at the time of LT, and AFP after LT, were compared as factors influencing HCC recurrence. We found that $\log_{10}$-transformed AFP values were significantly
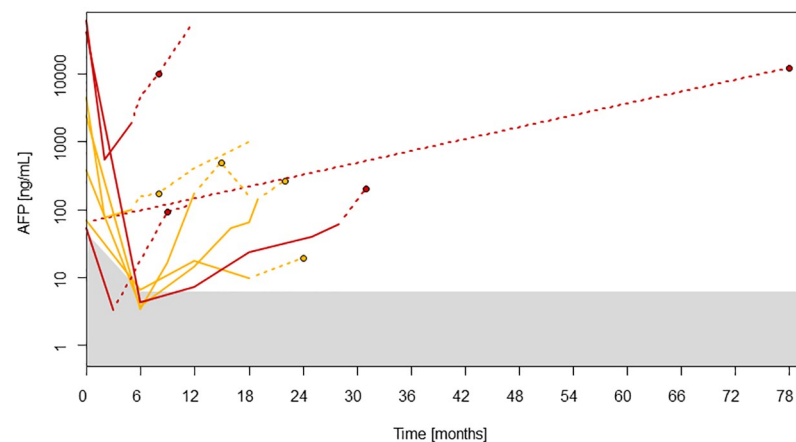

Fig 2. To illustrate AFP values of patients with HCC recurrence and AFP values above 50 ng/mL at LT, solid lines are used to indicate the course of AFP values until the last available measurement 3 months before diagnosis of recurrence, while the further course of AFP levels until diagnosis of HCC recurrence and thereafter is shown by dotted lines. Red lines and dots: patients with HCC recurrence in the liver; orange lines and dots: extrahepatic recurrence; dots: diagnosis of recurrence; shaded area: 90% percentile for non-recurrence.

https://doi.org/10.1371/journal.pone.0235576.g002
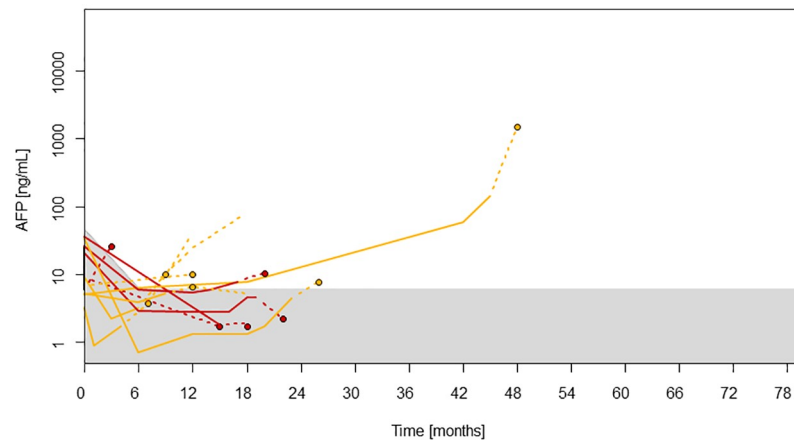
Fig 3. This graph shows the AFP values of patients with HCC recurrence and AFP values below 50 ng/mL at LT.
To focus on information available for recurrence prediction before diagnosis, solid lines are again used to illustrate the course of AFP values until the last available measurement 3 months before diagnosis of recurrence. Further course of AFP until diagnosis of recurrence and thereafter is shown by dotted lines. Red lines and dots: patients with HCC recurrence in the liver; orange lines and dots: extrahepatic recurrence; dots: diagnosis of recurrence; shaded area: 90% percentile for non-recurrence.

https://doi.org/10.1371/journal.pone.0235576.g003

associated with recurrence at the time of LT (HR 1.75, p = 0.023) as well as after LT (HR 2.07, p = 0.037).

AFP for prediction of survival after HCC recurrence

To determine the influence of different AFP values on survival after recurrence, we compared AFP levels at LT as well as 6 and 3 months before recurrence, at recurrence and after recurrence in a multivariate model. We found that the ratio of AFP at recurrence to AFP 3 months before recurrence was predictive for survival following HCC recurrence. Mortality risk was increased if AFP values were high at recurrence, and/or low 3 months before recurrence. Fig 4 shows the prediction of survival following HCC recurrence depending on the AFP ratio (p = 0.0232). Median survival in patients with a ratio (AFP at recurrence divided by AFP 3
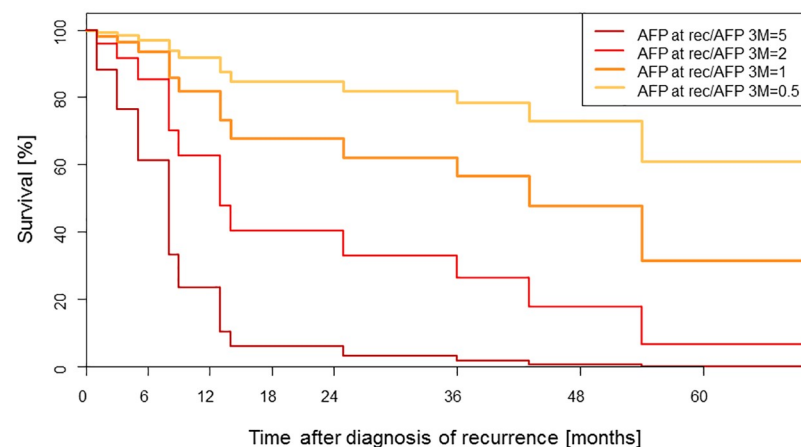

Fig 4. Prediction of survival after diagnosis of recurrence depending on AFP levels (p = 0.0232).

https://doi.org/10.1371/journal.pone.0235576.g004

months before recurrence) of 0.5 was greater than 70 months, as compared to a median of only 8 months in patients with a ratio of 5.

Clinical course and treatment of patients with HCC recurrence

Treatment of recurrent HCC after LT was done on a case by case basis, considering the individual patient´s performance status, liver graft function, and disease extent (metastatic pattern). Management decisions were made in an interdisciplinary approach by the local liver cancer and transplantation conference. The clinical course of all patients with HCC recurrence is listed in S1 Table. Systemic treatment approaches included sorafenib and ramucirumab, or tamoxifen and thalidomide in 13 patients treated before tyrosine kinase inhibitors were approved. Locoregional treatment was performed with transarterial chemoembolization (TACE), percutaneous microwave ablation (MWA) or radiofrequency ablation (RFA), respectively. In patients with resectable tumors, surgery was favored.

Discussion

Liver transplantation is a curative treatment option in patients with early HCC. However, a considerable number of patients experience HCC recurrence after LT. In the current study, we investigated the incidence of HCC recurrence after LT, in a high MELD area with correspondingly longer waiting times between listing for LT and graft allocation. Furthermore, a thorough risk analysis for HCC recurrence and mortality was performed, with a focus on the relevance of AFP measurements.

A major finding of our analysis is that both overall HCC recurrence rate and patient survival rate were comparable to other reports, including patients transplanted in countries from low MELD areas [9]. While a longer waiting time could be associated with progression and micrometastasis, a prolonged waiting time may also facilitate the detection of biologically more aggressive HCC nodules. As such, patients with rapidly progressive disease are less likely to receive a liver graft, which could explain the aforementioned observation of our study [23].

The second major finding is that AFP measurement is indeed justified in both LT candidates and recipients with HCC prior to LT. In general, serum AFP levels may be associated with HCC tumor mass, but not all HCC patients show high AFP levels, e.g. above 250–400 ng/ml. Besides, mild to moderate AFP elevations may be associated with hepatic necroinflammation independent of malignancy [24]. Thus, it may be assumed that a low AFP serum level prior to LT has limited informative value, but that high AFP levels prior to LT indicate a higher risk for HCC recurrence after LT. Indeed, several studies have reported an increased risk of HCC recurrence after LT in patients with higher AFP levels prior to transplant. Mazzaferro et al. described an HCC recurrence prediction model that includes absolute AFP values prior to LT [25]. Similarly, the MORAL score as published by Brown and colleagues used preoperative AFP values to estimate the HCC recurrence risk after LT [26]. Indeed, we were also able to confirm that AFP levels at LT are significantly correlated with HCC recurrence in our study.

The situation of HCC recurrence after LT, however, differs significantly from HCC development in liver cirrhosis. In patients with advanced liver disease, HCC nodules occur in a necroinflammatory environment of varying severity, mainly within a cirrhotic liver. In contrast, recurrent HCC nodules after LT mainly comprise metastatic lesions to the lungs, liver and bone, and the liver graft is generally not cirrhotic. While we did not observe an association between absolute AFP levels after LT and HCC recurrence, we did find that a rise in serum AFP levels occurred several months before radiological HCC diagnosis and moreover that the ratio of AFP levels at recurrence to AFP levels 3 months before recurrence was predictive for HCC survival after recurrence. Our observation is in concordance with another study,

reporting that the steepness ("slope") of an AFP rise was more important for prediction of recurrence than the value itself [27]. Our finding is clinical meaningful, because it is not only critical to know whether patients are at increased risk for HCC recurrence, but also to detect HCC recurrence as early as possible. Follow-up care of HCC in liver graft recipients has not yet been evaluated in prospective clinical trials. Some centers suggest three-monthly chest CT scans and CT or MRI scans of the liver, and optionally bone scintigraphy, to detect recurrent HCC [19,20,21]. However, performance of repeated CT scans in putatively cured patients are particularly questionable with respect to radiation exposure. The observation that AFP kinetics can be critically informative in the post-LT setting, even when absolute AFP values are comparatively low, may help to identify patients at increased short-term risk of HCC recurrence and thus requiring an intensified surveillance strategy [28–30].

Finally, we recorded treatment strategies and clinical outcomes in patients with recurrent HCC after LT. As no prospective studies are available investigating the optimal treatment of recurrent HCC after LT, treatment strategies are based on approaches in patients with HCC without a history of LT, and retrospective analyses in patients with HCC recurrence after LT [11]. As a consequence, the best treatment strategy for a given patient is currently determined by an individualized and multidisciplinary approach. Treatment options include surgery for localized disease, locoregional treatments such as TACE and radiofrequency ablation (RFA), and systemic treatments such as sorafenib [31].

Ramucirumab is a VEGF receptor-2 antagonist and was investigated in two large placebo-controlled phase III trials as second-line treatment in patients with HCC after treatment with sorafenib [32,33]. We have included two cases of patients with recurrent HCC after LT who were treated with ramucirumab after progression on sorafenib and multimodal treatment. Further trials are needed to evaluate the efficacy and toxicity profile of ramucirumab in this subgroup of patients. Furthermore, experience in the management of patients with recurrent HCC after LT is based on case reports, since these patients were excluded in the clinical trials. The incidence of side effects, toxicities and drug interactions, especially with immunosuppression, is therefore largely unknown.

The major limitation of our study is its limited sample size. Moreover, the retrospective and single-center design has to be taken into account. On the other hand, our cohort covers a period of almost 20 years. Although our data are reliable and the main findings are in concordance with other studies in this field, it is clear that conclusions from our data should be drawn very carefully.

In conclusion, our data indicate that HCC recurrence after LT is not increased, and patient survival is not decreased in a high MELD area with correspondingly longer waiting times for LT. A rise in AFP levels rather than the use of an absolute threshold could help to identify patients at short-term risk for HCC recurrence post LT. Thus, patients with increasing AFP levels after LT should be monitored closely for HCC recurrence and intensified follow-up should be considered.

Supporting information

S1 Table. Clinical course and treatment of patients with recurrent HCC after liver transplantation.
(DOCX)

S1 Data. Anonymized data set.
(XLSX)

Author Contributions

Conceptualization: Christine Koch, Theresa Bette, Natalie Filmann, Eva Herrmann, Martin-Walter Welker.

Data curation: Theresa Bette, Natalie Filmann, Eva Herrmann, Martin-Walter Welker.

Formal analysis: Christine Koch, Theresa Bette, Oliver Waidmann, Natalie Filmann, Christopher Schrecker, Jörg Trojan, Nina Weiler, Johannes Vermehren, Andreas A. Schnitzbauer, Wolf Otto Bechstein, Eva Herrmann, Martin-Walter Welker.

Investigation: Christine Koch, Theresa Bette, Natalie Filmann, Jörg Trojan, Martin-Walter Welker.

Methodology: Christine Koch, Oliver Waidmann, Natalie Filmann, Johannes Vermehren, Andreas A. Schnitzbauer, Wolf Otto Bechstein, Eva Herrmann, Martin-Walter Welker.

Project administration: Christine Koch, Stefan Zeuzem, Martin-Walter Welker.

Resources: Christopher Schrecker, Stefan Zeuzem, Eva Herrmann.

Software: Eva Herrmann.

Supervision: Christine Koch, Jörg Trojan, Andreas A. Schnitzbauer, Wolf Otto Bechstein, Stefan Zeuzem, Martin-Walter Welker.

Validation: Oliver Waidmann, Christopher Schrecker, Nina Weiler, Johannes Vermehren, Stefan Zeuzem, Eva Herrmann, Martin-Walter Welker.

Visualization: Theresa Bette, Nina Weiler, Eva Herrmann.

Writing – original draft: Christine Koch, Martin-Walter Welker.

Writing – review & editing: Christine Koch, Theresa Bette, Oliver Waidmann, Natalie Filmann, Christopher Schrecker, Jörg Trojan, Nina Weiler, Johannes Vermehren, Andreas A. Schnitzbauer, Wolf Otto Bechstein, Stefan Zeuzem, Eva Herrmann, Martin-Walter Welker.

References

1. Taniguchi M. Liver transplantation in the MELD era—analysis of the OPTN/UNOS registry. Clin Transpl. 2012 Jan;41–65. PMID: 23721009

2. Shukla A, Vadeyar H, Rela M, Shah S. Liver Transplantation: East versus West. J Clin Exp Hepatol. 2013 Sep; 3(3):243–53. https://doi.org/10.1016/j.jceh.2013.08.004 PMID: 25755506

3. Schoening WN, Buescher N, Rademacher S, Andreou A, Kuehn S, Neuhaus R, et al. Twenty-year longitudinal follow-up after orthotopic liver transplantation: a single-center experience of 313 consecutive cases. Am J Transpl. 2013 Sep; 13(9):2384–94.

4. Yoo HY, Patt CH, Geschwind JF, Thuluvath PJ. The outcome of liver transplantation in patients with hepatocellular carcinoma in the United States between 1988 and 2001: 5-year survival has improved significantly with time. J Clin Oncol. 2003; 21(0732-183X):4329–35. https://doi.org/10.1200/JCO.2003.11.137 PMID: 14581446

5. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996; 334:693–9. https://doi.org/10.1056/NEJM199603143341104 PMID: 8594428

6. Mazzaferro V, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol. 2009 Jan; 10(1474–5488 (Electronic) LA-eng PT-Journal Article SB-IM):35–43. https://doi.org/10.1016/S1470-2045(08)70284-5 PMID: 19058754

7. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology. 2001 Jun; 33(0270–9139 (Print)):1394–403. https://doi.org/10.1053/jhep.2001.24563 PMID: 11391528

8. DuBay D, Sandroussi C, Sandhu L, Cleary S, Guba M, Cattral MS, et al. Liver transplantation for advanced hepatocellular carcinoma using poor tumor differentiation on biopsy as an exclusion criterion. AnnSurg. 2011 Jan; 253(1528–1140 (Electronic)):166–72.

9. Welker M-W, Bechstein W-O, Zeuzem S, Trojan J. Recurrent hepatocellular carcinoma after liver transplantation—an emerging clinical challenge. Transpl Int. 2013 Feb; 26(2):109–18. https://doi.org/10.1111/j.1432-2277.2012.01562.x PMID: 22994652

10. Bruix J, da Fonseca LG, Reig M. Insights into the success and failure of systemic therapy for hepatocellular carcinoma. Nat Rev Gastroenterol Hepatol [Internet]. 2019 Aug 1 [cited 2019 Sep 2]; http://www.ncbi.nlm.nih.gov/pubmed/31371809

11. Welker M-W, Bechstein W-O, Zeuzem S, Trojan J. Recurrent hepatocellular carcinoma after liver transplantation—an emerging clinical challenge. Transpl Int. 2013 Feb; 26(2):109–18. https://doi.org/10.1111/j.1432-2277.2012.01562.x PMID: 22994652

12. Verna EC, Patel YA, Aggarwal A, Desai AP, Frenette C, Pillai AA, et al. Liver transplantation for hepatocellular carcinoma: Management after the transplant. Am J Transplant [Internet]. 2019 Dec 9 [cited 2019 Dec 11];ajt.15697. https://onlinelibrary.wiley.com/doi/abs/10.1111/ajt.15697

13. Foerster F, Hoppe-Lotichius M, Vollmar J, Marquardt JU, Weinmann A, Wörns MA, et al. Long-term observation of hepatocellular carcinoma recurrence after liver transplantation at a European transplantation centre. United Eur Gastroenterol J. 2019 Jul 1; 7(6):838–49.

14. Kondili LA, Lala A, Gunson B, Hubscher S, Olliff S, Elias E, et al. Primary hepatocellular cancer in the explanted liver: outcome of transplantation and risk factors for HCC recurrence. Eur J Surg Oncol [Internet]. 2007 Sep [cited 2019 Sep 3]; 33(7):868–73. Available from: http://www.ncbi.nlm.nih.gov/pubmed/17258882

15. Agopian VG, Harlander-Locke M, Zarrinpar A, Kaldas FM, Farmer DG, Yersiz H, et al. A novel prognostic nomogram accurately predicts hepatocellular carcinoma recurrence after liver transplantation: Analysis of 865 consecutive liver transplant recipients. In: Journal of the American College of Surgeons. Elsevier Inc.; 2015. p. 416–27.

16. Duvoux C, Roudot–Thoraval F, Decaens T, Pessione F, Badran H, Piardi T, et al. Liver Transplantation for Hepatocellular Carcinoma: A Model Including α-Fetoprotein Improves the Performance of Milan Criteria. Gastroenterology. 2012 Oct; 143(4):986–994.e3. https://doi.org/10.1053/j.gastro.2012.05.052 PMID: 22750200

17. Notarpaolo A, Layese R, Magistri P, Gambato M, Colledan M, Magini G, et al. Validation of the AFP model as a predictor of HCC recurrence in patients with viral hepatitis-related cirrhosis who had received a liver transplant for HCC. J Hepatol. 2017 Mar 1; 66(3):552–9. https://doi.org/10.1016/j.jhep.2016.10.038 PMID: 27899297

18. Filgueira NA. Hepatocellular carcinoma recurrence after liver transplantation: Risk factors, screening and clinical presentation. World J Hepatol. 2019 Mar 1; 11(3):261–72. https://doi.org/10.4254/wjh.v11.i3.261 PMID: 30967904

19. Zhang X, Li J, Shen F, Lau WY. Significance of presence of microvascular invasion in specimens obtained after surgical treatment of hepatocellular carcinoma. Vol. 33, Journal of Gastroenterology and Hepatology (Australia). Blackwell Publishing; 2018. p. 347–54.

20. Weiler N, Bilge N, Troetschler S, Vermehren J, Schnitzbauer AA, Herrmann E, et al. Conversion From Sirolimus to Everolimus in Long-Term Liver Graft Recipients. J Clin Pharmacol. 2017; 57(7):837–45. https://doi.org/10.1002/jcph.871 PMID: 28134984

21. Liese J, Peveling-Oberhag J, Doering C, Schnitzbauer AA, Herrmann E, Zangos S, et al. A possible role of microRNAs as predictive markers for the recurrence of hepatocellular carcinoma after liver transplantation. Transpl Int. 2016 Mar; 29(3):369–80. https://doi.org/10.1111/tri.12733 PMID: 26697811

22. Geissler EK, Schnitzbauer AA, Zülke C, Lamby PE, Proneth A, Duvoux C, et al. Sirolimus Use in Liver Transplant Recipients With Hepatocellular Carcinoma: A Randomized, Multicenter, Open-Label Phase 3 Trial.

23. Otto G, Schuchmann M, Hoppe-Lotichius M, Heise M, Weinmann A, Hansen T, et al. How to decide about liver transplantation in patients with hepatocellular carcinoma: Size and number of lesions or response to TACE? J Hepatol. 2013 Aug; 59(2):279–84. https://doi.org/10.1016/j.jhep.2013.04.006 PMID: 23587474

24. Huo T-I, Hsia C-Y, Chu C-J, Huang Y-H, Lui W-Y, Wu J-C, et al. The predictive ability of serum?-fetoprotein for hepatocellular carcinoma is linked with the characteristics of the target population at surveillance. J Surg Oncol. 2007 Jun; 95(8):645–51. https://doi.org/10.1002/jso.20653 PMID: 17530668

25. Mazzaferro V, Sposito C, Zhou J, Pinna AD, De Carlis L, Fan J, et al. Metroticket 2.0 Model for Analysis of Competing Risks of Death After Liver Transplantation for Hepatocellular Carcinoma. Gastroenterology. 2018 Jan 1; 154(1):128–39. https://doi.org/10.1053/j.gastro.2017.09.025 PMID: 28989060

26. Halazun KJ, Najjar M, Abdelmessih RM, Samstein B, Griesemer AD, Guarrera J V., et al. Recurrence after liver transplantation for hepatocellular carcinoma. Ann Surg. 2017 Mar 1; 265(3):557–64. https://doi.org/10.1097/SLA.0000000000001966 PMID: 27611615

27. Giard J-M, Mehta N, Dodge JL, Roberts JP, Yao FY. Alpha-Fetoprotein Slope >7.5 ng/mL per Month Predicts Microvascular Invasion and Tumor Recurrence After Liver Transplantation for Hepatocellular Carcinoma. Transplantation [Internet]. 2018 May 1 [cited 2019 Aug 21]; 102(5):816–22. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29505494

28. Burgio MD, Ronot M, Fuks D, Dondero F, Cauchy F, Gaujoux S, et al. Follow-up Imaging After Liver Transplantation Should Take Into Consideration Primary Hepatocellular Carcinoma Characteristics.

29. Hatzaras I, Bischof DA, Fahy B, Cosgrove D, Pawlik TM. Treatment Options and Surveillance Strategies After Therapy for Hepatocellular Carcinoma. Ann Surg Oncol. 2014 Mar; 21(3):758–66. https://doi.org/10.1245/s10434-013-3254-5 PMID: 24006095

30. Clavien P-A, Lesurtel M, Bossuyt PMM, Gores GJ, Langer B, Perrier A, et al. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol. 2012 Jan; 13(1):e11–22. https://doi.org/10.1016/S1470-2045(11)70175-9 PMID: 22047762

31. Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc J-F, et al. Sorafenib in Advanced Hepatocellular Carcinoma. N Engl J Med. 2008 Jul; 359(4):378–90. https://doi.org/10.1056/NEJMoa0708857 PMID: 18650514

32. Zhu AX, Kang YK, Yen CJ, Finn RS, Galle PR, Llovet JM, et al. No Title [Internet]. The Lancet Oncology Lancet Publishing Group; Feb 1, 2019 p. 282–96. https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(18)30937-9/fulltext

33. Zhu AXA, Park JO, Ryoo B-Y, Yen C-J, Poon R, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. 2015 Jul; 16(7):859–70.