Liver Transplantation for Extended Criteria Hepatocellular Carcinoma Using Stable Response to Locoregional Therapy and Alpha-Fetoprotein as Selection Criteria

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Keywords

Liver transplantation · Risk stratification · Tumor biology · Liver cancer · Overall survival

Abstract

Introduction: Current practice to only prioritize hepatocellular carcinoma (HCC) that fulfill the Milan criteria (IN_{MC}) is changing, since it causes the exclusion of patients who could benefit from liver transplantation. To select patients outside MC (OUT_{MC}) for transplantation, we implemented extended selection criteria without up-front morphometric restrictions containing surrogate parameters of tumor biology. **Methods:** OUT_{MC} patients were considered without restrictions of morphometrics and received locoregional treatment after interdisciplinary consultation. Our dynamic selection criteria for OUT_{MC} patients required (IN_{MUC}): (1) treatment response over (2) at least 6 months and (3) alpha-fetoprotein ≤400 ng/mL over the entire evaluation period. Patients with IN_{MC} tumors served as control and internal validation cohort. **Results:** 31 of 170 liver transplant candidates were OUT_{MC}. Of these, 8 dropped out. The remaining 23 patients met the selection criteria and underwent transplantation. Recurrence-free survival was higher in

patients transplanted IN_{MC} compared to those OUT_{MC} IN_{MUC} (92.2% vs. 70.8%; $p = 0.026$) after 5 years of follow-up. Overall survival showed no significant difference ($p = 0.552$). With dynamic selection of transplant candidates, recurrence could also be predicted for the IN_{MC} patients as internal validation cohort (c-index: 0.896; CI 0.588–0.981, $p = 0.005$). **Conclusion:** Dynamic selection criteria for the stratification of patients with OUT_{MC} HCCs is feasible and allows for excellent long-term results and acceptable tumor recurrence rates comparable to IN_{MC} patients.

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Introduction

Over the last 20 years, liver transplantation (LT) has established itself as the standard therapy for selected patients with hepatocellular carcinoma (HCC). Initial results after LT were poor, mainly due to lacking patient selection with excessive tumor burden and unknown tumor biology. It was not until 1996 that Mazzaferro et al. [1] defined tumor criteria (Milan criteria [MC]: single HCC ≤5 cm or up to 3 HCCs ≤3 cm) for patient selection. These criteria were associated with comparable outcomes

to patients receiving LT for other indications [1]. Since then, the MC have become standard and are widely used to prioritize patients on the LT waiting list. However, the application of MC excludes many patients with more and larger tumors who would similarly benefit from LT. Therefore, in recent years, many transplant groups have tried to define morphometric criteria beyond the limits of the MC that also resulted in good transplant outcomes. Among others, a well-known representative of these extended criteria are the University of California, San Francisco (UCSF) criteria (single lesion ≤ 6.5 cm, 2–3 lesions ≤ 4.5 cm with a total diameter ≤ 8 cm), which show comparable outcomes (5-year survival 72.4%), with similarly low recurrence rates (11.4%) as compared to the MC [2]. Therefore, it seems that mere morphometric criteria, at a random time point, only incompletely capture the individual tumor biology. Other surrogates of tumor biology may be more suitable to predict the individual tumor recurrence risk after transplantation. In recent publications it could be shown that increased alpha-fetoprotein (AFP) levels appear to indicate poor tumor biology. Although most patients have AFP values well below 200 ng/mL and the selected cut-off values vary between studies, they all have in common that tumor recurrence rates rise with increasing pre-LT AFP values [3–5]. Response to therapy was proposed by Otto et al. and confirmed by others as selection criterion reflecting tumor biology [6].

These principal ideas have found their way into the latest HCC clinical practice guidelines by the AASLD. The OPTN/UNOS policy guidelines for exception approval now include three criteria for IN_{MC} and OUT_{MC} patients. These are a (1) 6-month waiting time prior listing (2) for (OUT_{MC} only) successful downstaging to IN_{MC} and (3) $AFP < 1,000$ ng/mL (or AFP has fallen after treatment to levels below 500 ng/mL) at initial request [7, 8]. However, inclusion in the downstaging protocol is only granted to patients outside the MC that additionally fulfill morphometric criteria and have a single tumor ≤ 8 cm or multiple tumors with a total diameter ≤ 8 cm.

We have shared the opinion that morphometric criteria are a poor predictor of tumor biology for some time and therefore prospectively subjected our patients with tumors outside the MC (OUT_{MC}) to a clinical selection process that also combines waiting time, treatment response, and AFP as surrogates of tumor biology but deliberately disregards the number of lesions and tumor size.

Methods

This analysis was approved by the ethics committee of the University of Munich (# EK-LMU-19-395) and was conducted in accordance with the World Medical Association Declaration of Helsinki. All patients signed informed consent for the transplantation

and for the use of organs from rescue allocation (OUT_{MC}). For the analysis of the data, no separate informed consent was required. This analysis (although not a downstaging study) is in accordance with the reporting criteria for downstaging studies proposed by Parikh et al. [9]. Diagnosis of HCC was based on contrast-enhanced cross-sectional imaging according to the national transplant guidelines [10]. LT candidates were evaluated according to center standard. After approval of our interdisciplinary LT board, eligible patients (possible transplant candidate, no extrahepatic tumor manifestation, no macrovascular invasion) were evaluated for bridging therapy and listed for LT. Patients with HCCs inside MC (IN_{MC}) were listed with HCC MELD exception points in status “T” (transplantable) and were transplanted either through lab MELD or exception MELD allocation as soon as a donor organ became available. Patients with tumors that were OUT_{MC} on radiology, were set on hold in status “NT” (not transplantable) after being listed. At the end of the 6-month observation period, OUT_{MC} tumor patients were reevaluated and activated in status “T” when they met our predefined dynamic selection criteria (MUC): (1) stable treatment response (full or partial response or stable disease) over (2) at least 6 months and (3) $AFP \leq 400$ ng/mL at any time point prior to transplantation. They predominantly received organs from center-orientated rescue allocation. Progression of intrahepatic disease, the presence of extrahepatic disease, or rise in $AFP > 400$ ng/mL resulted in exclusion from consideration for LT OUT_{MC} .

In this report, the patients listed for LT because of HCC were analyzed according to morphometric criteria (MC) and their dynamic surrogates for tumor biology (MUC) (Fig. 1). The patient population consisted of the following four groups:

- 1 inside MC and inside MUC: $IN_{MC} IN_{MUC}$
- 2 inside MC and outside MUC: $IN_{MC} OUT_{MUC}$
- 3 outside MC and inside MUC: $OUT_{MC} IN_{MUC}$
- 4 outside MC and outside MUC: $OUT_{MC} OUT_{MUC}$

Patients $OUT_{MC} OUT_{MUC}$ were not transplanted according to our selection process, since transplantation was regarded as futile in those cases.

Almost all patients received locoregional bridging therapy (LRT) on a case-by-case basis as decided by our local multidisciplinary tumor board. LRT included radiofrequency ablation (RFA) drug-eluting bead transarterial chemoembolization (DEB-TACE), selective internal radiation therapy (SIRT). The decision was guided by the medical condition of the patient, their functional state, liver function, localization of the tumor, and patients’ preference. During the waiting period, tumor growth and AFP values were monitored at 3-month intervals. Response-to-therapy was evaluated according to the standardized modified Response Evaluation Criteria for Solid Tumors (mRECIST) criteria by contrast-enhanced, cross-sectional imaging. AFP was determined at recertification visits at least at baseline and prior to listing in status “T” [11].

After transplantation, patients received a standard immunosuppressive protocol with tacrolimus, MMF, and tapering dosages of steroids. In our center, it is practice that HCC patients switch to everolimus instead of or in combination with tacrolimus [12].

Statistical Analysis

The data on demographics, lab MELD and donor organ age, AFP level, bridging-to-transplant therapy, response-to-therapy (mRECIST), tumor stage, survival data, and the reason for death were obtained and stored in an Excel database (Microsoft Excel® for Mac, version 15.19, Microsoft Corporation, Redmond, WA, USA). Survival times for overall survival were calculated from the date of listing for transplantation to the date of death. Disease-free survival was calculated from the date of transplantation until the date of recurrence or death. Recurrence-free survival was calculated

Fig. 1. Dimensions of patient selection for LT against HCC. CR, complete remission; PR, partial response; SD, stable disease; AFP, alpha-fetoprotein.

Fig. 2. Patient population of the study. CR, complete remission; PR, partial response; SD, stable disease; AFP, alpha-fetoprotein.

from transplantation to the date of recurrence. Death without recurrence was censored. Comparison of continuous and categorical data was performed using the *t* test, Wilcoxon Rank sum test, and χ^2 test where applicable. Survivals were estimated using the Kaplan-Meier method. It was compared with the log-rank test (95% confidence interval [CI]). Variables for multivariate analysis were identified with the well-described Collett's model for selection [13]. For the multivariate analysis of all patients who were listed for transplantation, OUT_{MUC} was excluded as risk factor because OUT_{MC} OUT_{MUC} inherently had a worse survival after being excluded from transplantation.

To validate the surrogates for tumor biology, the results of IN_{MUC} and OUT_{MUC} were compared within the homogenous group of IN_{MC} patients. To assess the strength of discrimination of the MUC, concordance of all transplanted patients IN_{MC} was calculated [14]. This allowed for calculating the c-statistics within a

homogenous patient group that received the same treatment (Fig. 1). A *p* value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using RStudio software (RStudio, version 0.99.489, RStudio Inc., Boston, MA, USA), utilizing the survival, coxphw, and survminer packages [15].

Results

Between January 1, 2007 and December 31, 2017, 170 patients presenting with HCC without metastatic disease were included and listed for LT. Of these, 3 were excluded for protocol violation and/or incomplete data. 136 patients with IN_{MC} tumors were listed for LT with MELD

Table 1. Demographic data of the study cohort

Characteristic	Overall (n = 167)	Inside MC (n = 136)	Outside MC (n = 31)	p value
Age at listing, years, median (IQR)	57 (9.60)	57 (9.53)	56.5 (8.76)	0.167
Alpha-fetoprotein prior to LT, ng/mL, median (IQR)	7 (18.55)	7 (23.5)	7.4 (9.8)	0.332
Sex, n (%)				
Male	137 (82.03%)	110 (80.88%)	27 (87.10%)	0.416
Female	30 (18.00%)	26 (19.12%)	4 (12.90%)	
Cirrhosis, n (%)				0.147
Child-Turcotte-Pugh A	82 (49.1%)	63 (46.67%)	19 (61.29%)	
Child-Turcotte-Pugh B	63 (37.72%)	56 (41.48%)	7 (22.58%)	
Child-Turcotte-Pugh C	21 (12.57%)	16 (11.85%)	5 (16.12%)	
Cause of cirrhosis, n (%)				0.846
Hepatitis C	73 (43.71%)	60 (44.12%)	13 (41.94%)	
Hepatitis B	35 (20.96%)	28 (20.59%)	7 (22.58%)	
Alcohol	70 (41.91%)	57 (41.91%)	13 (41.94%)	
Other	23 (13.77%)	17 (12.5%)	6 (19.35%)	
Tumors at baseline, n (%)				<0.001
1	91 (54.49%)	84 (61.76%)	7 (22.58%)	
2	32 (19.16%)	23 (16.91%)	9 (29.03%)	
3	24 (14.37%)	18 (13.75%)	6 (19.35%)	
>3	9 (5.39%)	0 (0%)	9 (29.03%)	
Initial largest tumor diameter, mm, median (IQR)	26 (15.5)	24 (12)	40 (20.5)	
LRTs, n (%)				0.157
DEB-TACE	49 (35.77%)	38 (35.19%)	15 (51.72%)	
DEB-TACE followed by RFA	36 (26.28%)	31 (28.70%)	5 (17.24%)	
DEB-TACE combined with various treatments	29 (21.17%)	22 (20.37%)	7 (24.14%)	
RFA only	12 (8.76%)	12 (11.11%)	0 (0%)	
Other singular treatments (resection, SIRT, SBRT)	6 (4.38%)	4 (3.70%)	2 (6.90%)	
DEB-TACE per patients, n	2 (2)	2 (2)	2 (2)	0.677
Combinations	53 (47.32%)	44 (48.89%)	9 (40.90%)	
Response, n (%)				0.872
Complete remission (CR)	26 (15.76%)	23 (17.29%)	3 (9.68%)	
Partial response (PR)	13 (7.87%)	10 (7.52%)	3 (9.68%)	
Stable disease (SD)	86 (52.12%)	68 (51.13%)	17 (54.84%)	
Progressive disease (PD)	41 (24.85%)	32 (24.06%)	8 (25.81%)	
Delisted patients, n (%)	39 (23.35%)	31 (22.79%)	8 (25.81%)	0.721
^{lab} MELD at transplantation	12 (8)	12 (7)	12.5 (10.25)	0.969
Exception MELD at transplantation		25 (6)		
Size of lesions on pathology				<0.001
Inside MC	100 (78.13%)	95 (88.78%)	5 (23.81%)	
Outside MC	28 (21.88%)	11 (10.28%)	18 (85.71%)	
Reason for death after transplantation*				0.535
Recurrence	3 (10.34%)	2 (8.70%)	1 (16.67%)	
Sepsis	6 (20.69%)	6 (26.09%)	0 (%)	
Graft failure	5 (17.24%)	4 (17.39%)	1 (16.67%)	
Other various reasons	15 (51.24%)	11 (47.83%)	4 (66.67%)	

^{lab}MELD, laboratory Model of End-Stage Liver Disease; MC, Milan criteria; RFA, radiofrequency ablation; TACE, transarterial chemoembolization; SIRT, selective internal radiotherapy. * Percentages from patients who died after transplantation.

exception points and treated with LRT, 107 of them were transplanted. In the same period, 31 patients with OUT_{MC} tumors were listed for LT and treated with LRT; 23 of them were transplanted (Fig. 2). Altogether, a median of 34.7 (56.63) months of follow-up was available for the analysis of the patients.

Demographics and Tumor Characteristics

Demographics, clinical parameters, and tumor characteristics of the study population are listed in Table 1. The patient characteristics showed no significant differences concerning demographic factors, underlying diseases, and disease severity between the study groups. Patients OUT_{MC} had more and larger tumors than those

Fig. 3. Overall survival in HCC patients after transplantation divided by morphometric criteria (Milan criteria) ($p = 0.552$). MC, Milan criteria; MUC, dynamic selection criteria.

IN_{MC} ($p < 0.001$). Since patients OUT_{MC} were mostly transplanted with organs from the rescue allocation, donor age in this group was higher ($p = 0.04$). For IN_{MC} patients, median labMELD was 12 (7) and exception MELD was 25 (6). For patients transplanted OUT_{MC}, labMELD did not differ significantly from patients IN_{MC} (12.5 [10.25]; $p = 0.969$).

Clinical Course of the Study Cohort

As mentioned above, there was no prespecified treatment algorithm. IN_{MC} were treated for a median time span of 0.16 (5.02) months, whereas OUT_{MC} patients were treated for a median of 4.50 (5.76) months. This difference did not reach statistical significance ($p = 0.273$). DEB-TACE was the most common treatment. It was used in 35.19% ($n = 38$) IN_{MC} and 51.72% ($n = 15$) OUT_{MC} patients. IN_{MC} patients received a median 2 (2) and OUT_{MC} 2 (2) TACE interventions ($p = 0.677$). The second most frequently used bridging therapy was TACE immediately followed by RFA of the same lesions. In the IN_{MC} group, this treatment was conducted in 31 patients (28.70%) compared to 5 (17.24%) OUT_{MC}. Additionally, TACE was utilized in different combinations of treatments (e.g., SBRT, SIRT, or resection) or in a different sequence with RFA (e.g., repeated alternating treatment). This was the case for 22 (20.37%) IN_{MC} and 7 (24.14%) OUT_{MC} patients. RFA in a single session was done in 12 (11.11%) of IN_{MC} patients. No OUT_{MC} patient received RFA as a singular treatment. The bridging therapies used and the corresponding response rates are shown in Table 1. The applied bridging approaches showed an excellent tumor response in most cases. 75.75% of patients showed a complete or partial tumor response or at least a stable

disease after bridging. Forty patients (23.35%) who were already listed for LT as destination therapy were delisted after bridging therapy (Fig. 2). IN_{MC} patients waited 6.7 months (median) before being transplanted. Because of the mandatory waiting time, OUT_{MC} IN_{MUC} patients waited 10.1 months before receiving an organ.

Overall outcome for patients who received LT because of HCC was excellent. At 5 years of follow-up, 73.7% (63.4%; 81.5%) of patients were alive. 88.4% (78.3%; 94.0%) of patients were free from any recurrence of their disease.

Patient Outcome Divided by the Morphometric Milan Criteria

As shown in Table 1, bridging treatment and treatment response in patients IN_{MC} and OUT_{MC} were comparable. Patients OUT_{MC} IN_{MUC} who had successfully undergone the selection process showed inferiority in disease recurrence, which however did not translate to a difference in overall survival compared to patients transplanted IN_{MC}. Two patients (8.70%) IN_{MC} and one patient (16.67%) OUT_{MC} IN_{MUC} died after recurrence. Most patients died from sepsis, graft failure, or other reasons unrelated to the HCC malignancy (Table 1). Post-transplant 1-, 3-, and 5-year overall survival was 91.1% (83.6%; 95.3%), 81.5% (71.7%; 88.2%), and 73.9% (62.0%; 82.6%) for patients IN_{MC} and 86.7% (64.3%; 95.5%), 71.7% (47.3%; 86.2%), and 71.7% (47.3%; 86.2%) for patients OUT_{MC} IN_{MUC} ($p = 0.55$) (Fig. 3). The recurrence-free survival after transplantation at 1, 3, and 5 years in the group IN_{MC} was 99.0% (93.2%; 99.9%), 96.2% (88.5%; 98.8%), and 92.2% (81.7%; 96.8%). Disease recurrence OUT_{MC} IN_{MUC} was higher with survival rates of 95.0%

Fig. 4. Disease recurrence in HCC patients after transplantation divided by morphometric criteria (Milan criteria) ($p = 0.026$). MC, Milan criteria; MUC, dynamic selection criteria.

Fig. 5. Overall survival in HCC patients inside Milan criteria (IN_{MC}) after transplantation divided by MUC ($p = 0.033$). MUC, dynamic selection criteria.

(69.5%; 99.3%), 80.9% (80.9%; 93.5%), and 70.8% (37.7%; 88.5%) at 1, 3, and 5 years after transplantation ($p = 0.026$) (Fig. 4).

Internal Validation of MUC in Inside Milan Criteria Tumors

The MUC were validated internally in the group of IN_{MC} patients, to verify the prognostic value of this dynamic selection process. IN_{MC} patients are homogenous in relation to their morphometric characteristics (Fig. 1). The retrospective application of our selection criteria to

IN_{MC} tumor patients showed an even greater selectivity in terms of overall and recurrence-free survival. Post-transplant 1-, 3-, and 5-year overall survival was 92.0% (83.1%; 96.3%), 85.3% (74.2%; 91.9%), and 78.5% (65.2%; 87.2%) for patients $IN_{MC} IN_{MUC}$ and 82.4% (54.7%; 93.9%), 61.9% (33.6%; 81.0%), and 49.6% (19.7%; 73.8%) for patients $IN_{MC} OUT_{MUC}$, respectively (Fig. 5) ($p = 0.033$). Moreover, 5-year overall survival of patients $OUT_{MC} IN_{MUC}$ (see above) was higher compared to patients $IN_{MC} OUT_{MUC}$ (71.7% vs. 49.6%). This difference, however, was not significant ($p = 0.406$).

Fig. 6. Disease recurrence in HCC patients inside Milan criteria (IN_{MC}) after transplantation divided by MUC ($p = 0.005$). MUC, dynamic selection criteria.

Table 2. Multivariate analysis after Collett's model for selection including all patients listed for transplantation

	Overall survival				Recurrence-free survival			
	univariate analysis	multivariate analysis			univariate analysis	multivariate analysis		
	<i>p</i> value	HR	confidence interval	<i>p</i> value	<i>p</i> value	HR	confidence interval	<i>p</i> value
Beyond Milan	0.317	1.561	0.732–3.330	0.249	0.016	2.72	1.305–5.670	0.007
HCV infection	0.201	1.549	0.802–2.994	0.193	0.221	1.60	0.795–3.225	0.180
HBV infection	0.575	0.794	0.347–1.818	0.585	0.27	0.56	0.216–1.469	0.240

HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio.

Disease recurrence was significantly higher in patients IN_{MC} OUT_{MUC} as compared to IN_{MC} IN_{MUC} . One- and 3-year recurrence-free survival IN_{MC} IN_{MUC} was 97.6% (83.9%; 99.7%). At 5 years, recurrence-free survival was 95.1% (81.9%; 98.8%). IN_{MC} OUT_{MUC} recurrence-free survival was 94.1% (65.0%; 99.1%) at 1 year, 86.9% (56.6%; 96.6%) at 3 years, and 76.0% (40.4%; 92.0%) ($p = 0.005$) (Fig. 6).

To test the concordance probability, the c-statistics of the model was calculated for all transplanted patients IN_{MC} . Dynamic selection (MUC) strongly predicted the recurrence after transplantation (0.896; CI 0.588–0.981).

Multivariate Analysis

To analyze risk factors for overall and recurrence-free survival, univariate and multivariate analysis adjusted for age, ascites, gender, cirrhosis, HCV infection, HBV infection, alcoholic liver disease, microvascular invasion, tumor staging, and tumor grading was performed.

After applying Collett's model for selection on all patients listed for transplantation because of HCC, HCV, HBV infection, OUT_{MC} remained as negative predictive variables. Detailed results are depicted in Table 2.

When applying the same process (Collett's model for selection in multivariate analysis) to the internal validation cohort (patients transplanted IN_{MC} IN_{MUC} and IN_{MC} OUT_{MUC}), MUC showed itself to be independently predictive of recurrence (Table 3).

Discussion

LT is the optimal treatment for selected patients with HCC and cirrhosis. In theory, most patients without extrahepatic tumor growth or macrovascular invasion would benefit to a greater or lesser extent from LT [16]. Due to the shortage of organs, however, it is necessary to select those patients whose transplantation success is not

Table 3. Multivariate analysis after Collet's model for selection including all patients transplanted inside the Milan criteria

	Overall survival				Recurrence-free survival			
	univariate analysis	multivariate analysis			univariate analysis	multivariate analysis		
	<i>p</i> value	HR	confidence interval	<i>p</i> value	<i>p</i> value	HR	confidence interval	<i>p</i> value
Outside Munich criteria	0.033	2.787	1.104–7.035	0.3	0.005	6.621	1.080–40.60	0.041
HCV infection	0.173	1.693	0.708–4.046	0.237	0.08	4.91	0.527–45.74	0.1622
HBV infection	0.209	1.966	0.781–4.955	0.152	0.228	6.125	0.002–60.25	0.998

HBV, hepatitis B virus; HCV, hepatitis C virus; HR, hazard ratio.

endangered by an excessive rate of tumor recurrence. Up to now, patients were selected based on morphometric criteria that take into account the number and size of HCC lesions. The current transplantation standard, the MC, is based on a somewhat random morphometric definition [1]. Obviously, a few mm above or below the selected cut-off values will make no clinical difference in recurrence rate, which is already heterogeneous inside the MC group. Nonetheless, many patients are excluded from transplantation due to the presumed worse outcome in order to comply with this rigid measure. Additionally, HCC patients within the MC disproportionately benefit from exception MELD points. In our study, this is reflected by the short waiting time for IN_{MC} patients and their low _{lab}MELD. OUT_{MC} patients had a comparable _{lab}MELD but waited longer to be transplanted with significantly older organs. Because of these above-mentioned reasons, attempts have been made in recent years to push the limits for acceptable number and sizes of tumors (UCSF, Up-to-7, Toronto Criteria). When applying these criteria, recurrence rates remained relatively low but heterogeneous [2, 17, 18]. A recent study by Grat et al. [5] showed in a retrospective analysis that even within the expanded criteria (UCSF and Up-to-7), patients with an unfavorable outcome can be identified. This furthermore underlines that morphometric criteria may be a reasonable tool to draw the line in large cohorts but may not pertain to the individual patient. To predict for the single patient, the individual tumor biology must be considered [3, 6, 19–21].

In the meantime, some surrogates for the tumor biology of HCC in the context of LT have been recognized. The poor results of patients with high AFP values before transplantation are well documented and have found its way into the OPTN/UNOS selection criteria for LT [4, 8]. Also, continuously high pretransplant AFP values may be a hallmark of a metastatic state of HCC and may, therefore, be an indicator of poor tumor biology [5, 22]. AFP combined with tumor size and number at one arbitrary time point, however, is probably not enough to define in-

clusion and exclusion criteria. In a recent study, the authors could not find any net reclassification benefit using the Metroticket 2.0 criteria or the AFP model [23]. The response to therapy to an LRT procedure seems to have good predictive power for the survival of the patients [6, 24]. However, there is a discussion whether the favorable outcome after “downstaging” relates to a possibly better tumor biology or the decreased tumor burden [25]. Also, the general survival benefit of bridging-to-transplant procedures is still under investigation, while evidence is mounting that it reduces the dropout rate [26, 27]. The Toronto criteria are unique by including tumor grading obtained by biopsy, as poorly differentiated tumors are associated with an increased risk of recurrence even after transplantation [28]. The determination of tumor grading, however, is only possible by biopsy and carries its own risk for complications. The determination of FDG-PET behavior is in the same direction, whereby PET-positive tumors are characterized by poor differentiation and thus a higher recurrence rate [29]. Furthermore, the degree of inflammation seems to influence the recurrence rate of HCCs, which is expressed in the neutrophil/lymphocyte ratio, tumor-infiltrating leukocytes, or CRP value [30, 31]. These measures, however, are all static and are applied only at one time point prior to or, in case of tumor-infiltrating leukocytes, even after transplantation.

Therefore, it was repeatedly pointed out that it is also important to trace the “natural” behavior of the tumor for a certain time in order to get an idea of its tumor biology. Here, a 6-month follow-up has proven to be advantageous [19, 21].

To get as close as possible to the individual tumor biology, it therefore seems reasonable to triangulate the (most likely) tumor behavior with different surrogate markers. In this prospective treatment path (MUC), we have included 3 of the above mentioned and readily available predictive aspects: (1) Response-to-Therapy, (2) Test-of-Time, and (3) AFP. From this, we defined the MUC for transplantation of OUT_{MC} patients with a high chance of transplant benefit. These parameters, in part, are also res-

onating in the latest EASL clinical practice guidelines and the current OPTN allocation guidelines for HCC [8].

Our data show that patient selection in HCCs limited to the liver without upfront restriction of morphometric criteria and with the guidance of surrogate markers of tumor biology may allow a better assessment of the individual risk of tumor recurrence. Even in patients OUT_{MC} IN_{MUC}, the tumor recurrence rates were in an acceptable range [32]. In our opinion, these differences are too small to exclude patients with tumors OUT_{MC} from LT with a high likelihood of long-term survival. Furthermore, only one (16.67%) patient in the OUT_{MC} IN_{MUC} group died due to recurrence. Compared to 8.70% (two patients) after IN_{MC}, this was higher. However, due to the small sample size no statistical difference could be detected. The retrospective application of our selection criteria in the IN_{MC} cohort, for validation, shows that there are also considerable differences within this group with regard to the risk of tumor recurrence. C-statistics and multivariate analysis showed that MUC selection strongly predicted recurrence after transplantation IN_{MC}. This result is especially interesting since all IN_{MC} patients received the same treatment and were already selected for a better outcome.

This work has limitations. Mainly, this is a single-center study with a relatively low number of included patients. However, since the selection of transplant-eligible patients OUT_{MC} is left to the individual centers, our dynamic selection criteria were only applied in ours. Furthermore, only patients who are considered transplantable and suitable for the dynamic selection criteria are included in this study. This combined with the fact that the OUT_{MC} OUT_{MUC} comparison group is de facto not existent, because these patients were excluded from LT, creates a selection bias. Therefore, the c-statistics could not be calculated for the group of patients OUT_{MC}, but only for IN_{MC} patients.

Whether criteria based solely on clinical monitoring of tumors in combination with tumor markers provide comparable or better results than traditional morphometric criteria for the entire HCC cohort must be clarified by prospective studies since a higher tumor burden in itself also carries a risk for worse tumor biology. These, however, are not available at this point [9]. A further advantage of dispensing with morphometric criteria when awarding standard exception points is the better auditability, traceability, and acceptance of tumor progression monitoring.

In conclusion, our dynamic selection process (MUC) is based solely on surrogate markers of tumor biology and does not require the determination of the number and size of tumors. Our data prove that such a selection process is feasible and leads to acceptable results for tumors OUT_{MC} as for tumors IN_{MC}. We are therefore advocating a change in the allocation system for HCC patients that takes individual tumor biology into account.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The need for an informed consent was waived for the data analysis.

Disclosure Statement

The authors have no conflicts of interest to declare.

Funding Sources

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Author Contributions

Markus Bo Schoenberg: contributed substantially to the conception and design of the study; acquisition, analysis, and interpretation of the data; drafted the manuscript; provided final approval of the version to be published. Hubertus Johann Wolfgang Anger: contributed substantially to the acquisition of the data; interpretation of the data; provided critical revision of the manuscript; provided final approval of the version to be published. Julian Nikolaus Bucher: contributed substantially to the acquisition of the data; interpretation of the data; provided critical revision of the manuscript; provided final approval of the version to be published. Gerald Denk: contributed substantially to the acquisition of the data; interpretation of the data; provided critical revision of the manuscript; provided final approval of the version to be published. Enrico De Toni: contributed substantially to the acquisition of the data; interpretation of the data; provided critical revision of the manuscript; provided final approval of the version to be published. Max Seidensticker: contributed substantially to the acquisition of the data; interpretation of the data; provided critical revision of the manuscript; provided final approval of the version to be published. Joachim Andrassy: contributed substantially to the acquisition of the data; interpretation of the data; provided critical revision of the manuscript; provided final approval of the version to be published. Martin Kurt Angele: contributed substantially to the acquisition of the data; interpretation of the data; provided critical revision of the manuscript; provided final approval of the version to be published. Jens Werner: contributed substantially to the conception and design of the study, acquisition, analysis and interpretation of the data; drafting and revision of the manuscript; provided final approval of the version to be published. Markus Otto Guba: contributed substantially to the conception and design of the study, acquisition, analysis and interpretation of the data; drafting and revision of the manuscript; provided final approval of the version to be published.

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