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Liver transplantation for HCC in cirrhosis: Are Milan criteria outdated?

Lebertransplantation bei HCC: Sind Milan-Kriterien überholt?

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Bibliography

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ABSTRACT

In Germany, organ allocation is based on the MELD-system and lab-MELD is usually low in patients with hepatocellular carcinoma (HCC) in cirrhosis. Higher medical urgency can be achieved by standard exception for HCC (SE-HCC), if Milan criteria (MC) are met. Noteworthy, UNOS T2 reflects MC, but excludes singular lesions < 2 cm. Thus, SE-HCC is awarded to patients with one lesion between 2 and 5 cm or 2 to 3 lesions between 1 and 3 cm. These criteria are static and do not reflect biological properties of HCC.

We present a retrospective cohort of 111 patients, who underwent liver transplantation at UKSH, Campus Kiel between 2007 and 2017. No difference was found in overall survival for patient cohorts using Milan, UCSF, up-to-seven, and French-AFP criteria. However, there was a significantly reduced survival, if microvascular invasion was detected in the explanted organ and in patients with HCC-recurrence. The exclusive use of static selection criteria including MC appear to limit the access to liver transplantation.

ZUSAMMENFASSUNG

Die Organallokation zur Lebertransplantation in Deutschland basiert auf dem MELD-System. Patienten mit einem hepatozellulären Karzinom (HCC) in Zirrhose weisen meist einen niedrigen laborchemischen (lab-)MELD auf. Eine Priorisierung der Dringlichkeit auf der Warteliste kann durch eine Standard-Exception (SE-HCC) erfolgen, wenn die Milan-Kriterien (MC) erfüllt sind. Die Richtlinie verwendet UNOS T2, welche MC entsprechen aber singuläre Tumoren unter 2 cm ausschließen. Die Priorisierung erfolgt nach rein statischen Kriterien und berücksichtigt keine weiteren biologischen Tumoreigenschaften.

In einer retrospektiven Studie analysierten wir 111 Patienten, die zwischen 2007 und 2017 am UKSH, Campus http://Kiel, transplantiert wurden. Das Gesamt-Überleben der Patienten unterteilt nach Milan-, UCSF-, up-to-seven- sowie French-

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AFP-Kriterien zeigte keine signifikanten Unterschiede. Demgegenüber fand sich bei mikrovaskulärer Invasion im Explantat sowie in der Rezidiv-Situation ein signifikant schlechteres Gesamtüberleben.

Die ausschließliche Verwendung statischer Selektionskriterien einschließlich MC impliziert einen eingeschränkten Zugang zur Lebertransplantation.

Introduction

Liver cancer marks the 6th world leading diagnosis for cancer and the 3rd leading diagnosis for cancer related deaths in the world [1]. Hepatocellular carcinoma (HCC) comprises 75–85 % of the cases [1]. In 2023, 41,210 new diagnosed cases and 29,380 deaths are expected by liver and intrahepatic bile duct cancer in the USA marking HCC a major global health burden. While 5-year relative survival rates have improved from 3 % in the 1970 s to 21 % up to 2018 ([2], therapeutic treatment needs to be improved. HCC in cirrhosis is one of the leading indications for liver transplantation (LT). LT is a cornerstone in HCC treatment and it also eliminates the regularly underlying cirrhotic disease of the liver. However, LT is limited to tumor stages, excluded for patients with extrahepatic spread (M+) and/or with macrovascular invasion (V2).

The quantum on donor organs determines the utilization. In many countries, especially in the Eurotransplant region, patients with HCC receive additional points on the LT waiting list, the so-called standard exception (SE-HCC), as long as tumor limits are within the United Network for Organ Sharing (UNOS) criteria T2. In contrast to Milan criteria (MC), UNOS T2 excludes lesions smaller 2 cm. Thus, lesions greater than or equal to 2 cm and less than or equal to 5 cm, as well as 2 to 3 lesions, each greater than or equal to 1 cm and less than or equal to 3 cm are included in the Milan criteria [3]. Lesions smaller 1 cm in contrast enhanced (CE)-MRI or CE-CT are excluded due to diagnostic uncertainty. However, in the allocation based on the UNOS classification, downsizing into the UNOS criteria, i. e. tumor reduction under locoregional therapy, is permitted and enables secondary receipt of SE-HCC. The inclusion of biological response demonstrates a combined use of dynamic and static selection criteria.

There are already many reports that the indications for LT within the MC are too restrictive [4, 5]: Comparable patient survival rates were described outside MC criteria, for example within the UCSF (*University of California, San Francisco*) or up-to-seven criteria [5]. The UCSF classification is also calculated from tumor size and number of tumors, but the cut-off values are not as strict as with the MC. The patient may have either 1 tumor lesion ≤ 6.5 cm, or ≤ 3 tumor lesions, each ≤ 4.5 cm. In addition, the total diameter of 8 cm must not be exceeded [6]. The calculation of the up-to-seven criteria is also based on static selection: They are determined from the sum of the number of tumor foci and size from the largest tumor lesion. This must be ≤ 7 [7]. In addition, the French AFP score was introduced using alpha-fetoprotein (AFP) as a biomarker for HCC [8]. However, AFP is not positive in all HCC cases. Besides AFP, tumor biology assessed by tumor response over time can be used as a dynamic selection criterion. Most patients undergo bridging therapy and a proof-of-time can be used to select potential transplant candidates with favorable tumor biology represented by absence of progressive disease. The integration of dynamic selection is already routine in the UNOS region [9]. For reasons of donor organ shortage, UNOS T2 is still the common practice for selection in Germany. In this retrospective analysis, we compared our institutional results on LT outcomes using different static selection criteria for patients with HCC.

Patients & Methods

In a retrospective analysis, we analyzed a group of patients who underwent LT at our center for the diagnosis of HCC between February 2006 and July 2017. The analysis includes the collection of transplantation criteria, previous illnesses, postoperative complications and survival data until August 2023 from the clinical information system. The patient collective was divided into the subgroups Milan-In, UCSF-In, French AFP high-risk and up-to-seven-In. As with the classification into Milan-In and Milan-Out, the tumor characteristics of the radiological diagnostics were used for the initial diagnosis.

The French AFP score was published in 2012 and is the first scoring system that uses a serum marker (AFP) for evaluation. It is based on a point system consisting of tumor size, tumor number and AFP cut-off level [8]. A simplified model of the French AFP high-risk score was used, as represented in ▶ **Table 1**, to classify the patient collective in this work: For each of the three categories, the patient received between 0 and 3 points. The collective was then divided into 2 groups based on the number of points achieved: AFP score > 2 or AFP score ≤ 2. An AFP score > 2 was considered “high-risk”. Also, Eurotransplant data were retrieved to compare our center results with Eurotransplant data.

The statistical data analysis was performed with the software GraphPad Prism 10, Graphpad Software, Inc, Boston, USA. The

▶ **Table 1** Simplified presentation of the AFP model.

variable	range	points
tumor size	≤ 3 cm	0
	3–6 cm	1
	> 6 cm	4
tumor lesions (n)	1–3	0
	≥ 4	2
AFP level	≤ 100 mg/ml	0
	100–1000 mg/ml	2
	> 1000	3

▶ **Table 2** Distribution within the classification systems, recurrence rate as well as death and time to death after liver transplantation.

	total number	recurrence	death	time to death after LT
tumor criteria	**patients (% of entire cohort)**	**patients (%)**	**patients (%)**	**median [months (range)]**
Milan-In	77 (69.4)	6 (7.8)	33 (42.9)	40.0 (0–172)
Milan-Out	34 (30.6)	12 (35.3)	19 (55.9)	32.5 (0–134)
UCSF-In	88 (79.3)	8 (9.1)	34 (38.6)	40.0 (0–172)
UCSF-Out	23 (20.7)	10 (43.5)	14 (60.9)	34.0 (0–134)
up-to-seven-In	76 (68.5)	7 (9.2)	32 (42.1)	40.0 (0–172)
up-to-seven-Out	35 (31.5)	11 (31.4)	20 (57.1)	39.0 (0–137)
French AFP low-risk	82 (73.9)	9 (11.0)	38 (46.3)	41.0 (0–134)
French AFP high-risk	29 (26.1)	9 (31.0)	14 (48.3)	40.0 (0–172)

evaluation of descriptive data and calculations of survival times as well as the influence of various parameters was carried out using Kaplan-Meier survival curves, significant differences were determined using log-rank tests. The level of significance was set at $p < 0.05$ for all variables tested.

Results

From February 2006 to July 2017, 111 LT for HCC were performed. The median patient age was 61 years (14 – 73 years). Of the patients, 26 were female (23.4 %). The median time on the waiting list was 4 months (0 – 66 months). Of the cohort, 106 patients (95.5 %) had a cirrhosis as underlying disease. The most common cause of liver cirrhosis was hepatitis infection at 49.5 % (hepatitis C in 21.6 % and hepatitis B in 12.6 %), followed by alcoholic cirrhosis at 36.9 %. Ascites was present or developed in 44 patients (39.6 %). After initial diagnosis of liver cirrhosis, 65 patients (58.6 %) developed portal hypertension. Of these, 17 patients (26.2 %) subsequently suffered variceal bleeding. The most common pre-existing conditions were arterial hypertension in 65 cases (58.6 %), diabetes mellitus in 53 cases (47.7 %), coronary heart disease in 16 cases (14.4 %) and other oncological diagnoses in 15 cases (13.5 %).

Preoperatively determined number of tumor lesions were n = 1 lesion in 70 cases, n = 2 lesions in 16 cases, n = 3 lesions in 16 cases, n = 4 lesions in 4 cases and n≥ 5 lesions in 5 cases. Approximately 16 % of all measured tumor foci were > 5 cm in size and 84 % were < 5 cm. In total, tumor lesions were found > 8 cm in diameter in 7 cases, > 5 cm and < 8 cm in 16 cases, lesions > 3 cm in 36 cases, lesions > 2 cm in 36 cases and lesions < 2 cm in 52 cases. Tumor classification is represented in ▶ **Table 2**. In brief, Milan-Out, UCSF-Out and up-to-seven-Out were found in 30.6 %, 20.7 % and 31.5 % of the cases, respectively. With an average AFP value of 706 mg/mL, elevated AFP levels were found in 56.8 % of patients at initial diagnosis. The value ranged from a minimum of 7.2 mg/mL to a maximum of 8,335 mg/mL. The subsequent calculation of the French AFP score revealed 29 patients (26.1 %) in the high-risk group. Detailed information on tumor sizes and number of lesions at initial diagnosis, just before LT as well as histopathological findings is depicted in ▶ **Table 3**. In 98 patients (88.3 %), a bridging procedure was used prior to LT. The predominantly performed procedure was transarterial chemoembolization (TACE) in 55 patients (49.5 %). Standard exception points on the waiting list (match-MELD) were granted for 51 patients (46.0 %).

The histopathological assessment revealed tumor differentiation from well differentiated (G1) in 18 cases (16.2 %), intermediate differentiated (G2) in 53 cases (47.8 %), poorly differentiated (G3) in 6 cases (5.4 %) and unknown differentiation in 34 cases (30.6 %). Microvascular invasion (V1) was found in 13 cases (11.7 %). In the patient collective, a total of 15 (13.5 %) patients received a re-transplantation, of which 9 patients received re-transplantation within the first month after LT.

The median follow-up was 82.5 months (0–205 months) with a maximum survival after transplantation of 17 years. During the follow-up, 18 patients with a median time after LT of 42 months (2–130 months) suffered a tumor recurrence and 17 patients died of the recurrence. In the Milan-In cohort (n = 77), 6 patients with a median time after LThttp:// of 44 months (4–130 months) suffered recurrence and all of them died during the follow-up. In the UCSF-In cohort (n = 88), 8 patients with a median time after LT of 42 months (10–130 months) suffered recurrence and all of them died. In the French AFP high-risk cohort (n = 29), 9 patients suffered recurrence after a median time of 48.5 months (2–118 months) and 6 of them died during the follow-up. In the up-to-seven-In cohort (n = 77), 7 patients suffered recurrence after a median time after LT of 49 months (10–130 months) and 5 of them died during the follow-up. A total of 51 patients (46.0 %) died after LT for HCC in this cohort with a median time after LT of 23 months (0–141 months). 36 patients (32.4 %) died of non-HCC related causes. ▶ **Table 2** gives detailed information on tumor recurrence, death and time from LT to death. Overall survival was not statistically significantly different for patients within or outside the Milan, UCSF, French AFP, or up-to-seven classification (▶ **Fig. 1A–D**), and with or without evidence of AFP (p = .955). Nevertheless, overall survival was significantly reduced in patients

▶ **Table 3** Tumor size and number of lesions at initial diagnosis, in last imaging before transplantation and after liver transplantation.

	initial diagnosis		before liver transplantation		after liver transplantation	
	size	number	size	number	size	number
tumor criteria	median [cm (range)]	median (range)	median [cm (range)]	median (range)	median [cm (range)]	median (range)
Milan-In	2.4 (0.4–4.8)	1 (1–3)	1.7 (0–4.8)	1 (0–5)	1.8 (0–9.5)	1 (0–8)
Milan-Out	5.0 (1.8–16.0)	2 (1–7)	2.9 (0–12.0)	2 (0–5)	3.8 (0–14.0)	2 (0–6)
UCSF-In	2.7 (0.4–6.5)	1 (1–3)	1.9 (0–9.5)	1 (0–5)	1.9 (0–9.5)	1 (0–8)
UCSF-Out	5.0 (1.8–16.0)	3 (1–7)	3.3 (0–12.0)	2 (0–5)	4.2 (0–14.0)	3 (0–6)
up-to-seven-In	2.7 (0.4–6.0)	1 (1–3)	1.6 (0–4.8)	1 (0–5)	1.6 (0–9.5)	1 (0–7)
up-to-seven-Out	4.3 (1.8–16.0)	3 (1–7)	3.3 (0–12.0)	2 (0–5)	4.0 (0–14.0)	2 (0–8)
AFP low-risk	2.65 (0.4–6.0)	1 (1–5)	1.7 (0–9.5)	1 (0–5)	1.9 (0–9.5)	1 (0–8)
AFP high-risk	4.8 (1.8–16.0)	2 (1–7)	3.3 (0–12.0)	2 (0–5)	3.5 (0–14.0)	2 (0–6)

with microvascular invasion (V1) as well as in patients with tumor recurrence (▶ **Fig. 1E** & **F**). ▶ **Table 4** provides an overview of 5-year, 10-year and overall survival.

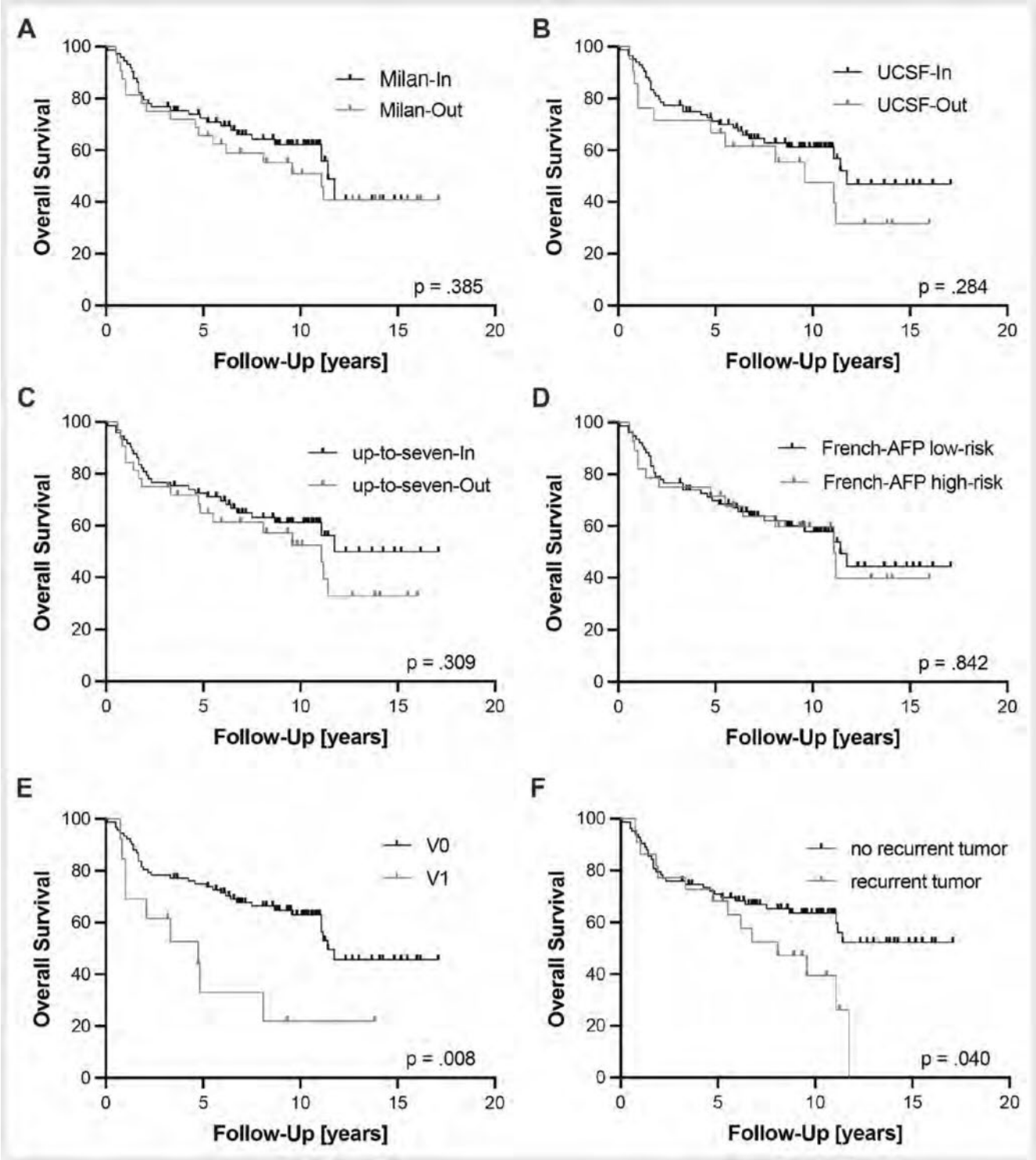
To validate our institutional data set, we compared our data to Eurotransplant data. The Eurotransplant analysis for waiting list mortality in Germany for the years 2007–2017 shows a lower mortality in patients with SE-HCC compared to other diagnosis and no SE-HCC. The 1-, 2- and 3-year waiting list mortality was 13 %, 16 % and 17 % for patients with SE-HCC, 18 %, 21 % and 23 % for patients without HCC and 19 %, 24 % and 26 % for patients with HCC but without SE-HCC. The 3-year estimated recipient survival for first transplants in Germany was 60 % for HCC-patients with no SE-HCC, 70 % for HCC-patients with SE-HCC, as well as for patients with no HCC and no SE and 80 % for SE-patients with no HCC. The Eurotransplant data show a 10 % different survival between recipients with or without SE-HCC. In contrast, our institutional data including retransplantation revealed no significant difference in the patient survival rate (▶ **Fig. 1A**, p = .385).

Discussion

Our data on LT for HCC show no significant difference in 5-year, 10-year and overall survival for patients within and outside MC. In addition, overall survival of patients with extended criteria using UCSF, French AFP high-risk- and up-to-seven-criteria was also not significant. Reports on 10-year and overall survival for patients with HCC after LT are rare. Just recently, international multicenter analyses from the CTS Collaborative Transplant Study at Heidelberg University showed a 10-year survival of 63 % in a cohort of 56,433 liver transplant patients. (CTS Newsletter 4:2023). This data will provide further interesting insights into the mortality statistics of patients after LT, particularly in patients with HCC, and remains exciting to see. Importantly, patient survival negatively affected by microvascular invasion and tumor recurrence in our cohort. Of note, our data is not corrected to tumor or transplant associated deaths and might be biased in this respect.

The corresponding Eurotransplant data for the period show a higher waiting list mortality for HCC-patients without SE-HCC compared to HCC-patients with SE-HCC and patients with other diagnosis. These findings underscore the ongoing discussion on allocation rules in Germany and the prioritization of different subgroups. The subgroup of HCC-patients without SE-HCC appears to be underrepresented, since these patients achieve similar results to SE-HCC patients. The possibility of serving patients with the best therapeutic option is limited by available organs.

Patients outside MC do not have prioritized access to donor organs. Therefore, grafts from extended criteria donors (ECD) have to be considered for MC-out patients to be transplanted in time. Despite liberal acceptance of ECD-grafts, we have not yet observed significant difference in donor risk index and graft failure within or outside MC [4]. While guidelines in Germany do not allow SE-HCC for MC-Out patients once downsizing is achieved, these patients can be transplanted, unless they have no extrahepatic tumor spread and no macrovascular invasion (V2). Of note, we selected these patients for LT eligibility as long as they had no progressive disease under locoregional therapy. In contrast, in UNOS regions, downsizing into UNOS T2 justifies a SE-HCC. The introduction of downsizing refines the previous static selection by addition of dynamic parameters to improve the selection of LT candidates that will have long time prognosis. The current version of the *Barcelona clinical liver cancer* (BCLC) staging criteria was adjusted and shifted treatment strategies towards LT [10]. BCLC was intended to consider tumor stage, liver function and patient general status [11]. While this system is still the basis of many therapy recommendations, it is limited by its strict categorization and the differences in local center performance. In a real-world analysis, center-based tumor board therapy recommendations and treatment data from over 300 patients with HCC were compared to BCLC staging criteria. LT was performed over all BCLC stages and individual center performance resulted in superior outcomes [12]. Such analyses led to the concept of *treatment stage migration*



▶ **Fig. 1** Kaplan-Meier analysis for overall survival in dependence of (**A**) Milan-, (**B**) UCSF-, (**C**) up-to-seven-criteria as well as (**D**) French-AFP low-risk and high-risk groups. Furthermore, significantly reduced overall survival for patients with (**E**) microvascular invasion and (**F**) patients suffering recurrence after LT are presented.

covering the tumor behavior under locoregional therapy (e. g. progressive, regressive or stable disease according to mRECIST criteria). The BCLC update includes the shift from one therapeutic option to another if the proposed therapy is not the optimal treatment for the individual patient [10].

In a comprehensive review, Lerut *et al.* proposed that 31 % more patients could be transplanted without negative impact on oncological outcome and overall survival, if "new" less restrictive allocation criteria would be applied [5]. Lai *et al.* showed the importance of adding biological tumor aspects to discriminate be-

▶ **Table 4** 5-year, 10-year and overall survival rate after liver transplantation.

	5-year survival		10-year survival		Overall survival	
tumor criteria	**patients (%)**	**p-value**	**patients (%)**	**p-value**	**patients (%)**	**p-value**
Milan-In	72.4		62.1		40.8	
Milan-Out	65.6	.465	50.9	.339	40.8	.415
UCSF-In	83.9		61.2		46.9	
UCSF-Out	77.6	.661	47.5	.358	31.7	.176
up-to-seven-In	81.7		61.2		50.0	
up-to-seven-Out	84.1	.619	52.4	.476	32.8	.162
French AFP low-risk	84.7		57.9		44.4	
French AFP high-risk	75.9	.430	59.7	.990	39.8	.923
V0	84.7		63.0		45.7	
V1	66.7	.178	22.0	**.003**	22.0	**.028**
no recurrent tumor	83.8		63.5		52.3	
recurrent tumor	77.3	.496	27.5	**.029**	0	**.025**

tween high- and low-risk patients for recurrence. In particular, tumor biology seems to be decisive for prognosis after LT [13]. In addition to grading and microvascular infiltration [14], the response to locoregional therapy is an important prognostic predictor [13]. Furthermore, the identification of patients with an increased risk of recurrence after resection is also important, because nearly half of the patients with early -stage HCC experience recurrence after resection mainly within 2 years after surgery [15]. In this context, the *ab initio* concept suggests listing after resection in patients with high risk of recurrence, before recurrence develops. Histopathological risk factors for recurrence include microvascular invasion and/or satellites. The listing shall be performed after a postoperative run-in phase of 6 months as long as no recurrence has occurred within this monitoring period. Early recurrence within 6 months of resection is associated with aggressive tumors that easily exceed LT criteria and should therefore not be transplanted [16]. On the other hand, the salvage LT is a concept to delay LT until recurrence occurs [17]. This salvage concept is particularly suitable for patients with HCC in cirrhosis without portal hypertension. The risk of recurrence after resection of an HCC in cirrhosis is up to 70 % within 5 years [18]. This finding was recently updated in a multicenter intention-to-treat analysis: The risk of recurrence after resection of an HCC in cirrhosis was significantly higher in the propensity scored matched liver resection group compared to the LT cohort after 5 years with 6.4 % versus 52.7 % [19]. The term recurrence covers 3 different entities: local recurrences, intrahepatic metastases and *de novo* tumors. A 2-year limit has been established to distinguish recurrences from *de novo* tumors. Salvage-LT thus offers an option for intrahepatic recurrence within a period of 2 years after liver resection.

However, our study is limited by its retrospective character and the small single center cohort.

In conclusion, the allocation of organs solely based on the MC (UNOS T2) criteria needs to be redefined and does not appear justified in view of the comparable survival data of patients within and outside of these restricted tumor stage. Our data implicate that individual tumor characteristics, such as microvascular infiltration, should be considered more carefully and should be investigated in studies. Furthermore, the effect of dynamic selection can be evaluated using the Toronto criteria that exclude V2, M+ and G3 after biopsy of the largest lesion to gain better understanding of individual tumor biology.

Conflict of Interest

The authors declare that they have no conflict of interest.

Literatur

[1] Sung H, Ferlay J, Siegel RL et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA A Cancer J Clin 2021; 71 (3): 209–249. doi:10.3322/caac.21660

[2] Siegel RL, Miller KD, Wagle NS et al. Cancer statistics, 2023. CA A Cancer J Clinicians 2023; 73 (1): 17–48. doi:10.3322/caac.21763

[3] Mazzaferro V, Regalia E, Doci R et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996; 334 (11): 693–699

[4] Gundlach JP, Linecker M, Dobbermann H et al. Patients Benefit from Liver Transplantation for Hepatocellular Carcinoma beyond Milan Criteria without Harming the Health Care System. Cancers 2022; 14 (5): 1136

[5] Lerut J, Foguenne M, Lai Q. Hepatocellular cancer selection systems and liver transplantation: from the tower of babel to an ideal comprehensive score. Updates Surg 2021; 73 (5): 1599–1614

[6] Yao F. Liver transplantation for hepatocellular carcinoma: Expansion of the tumor size limits does not adversely impact survival. Hepatology 2001; 33 (6): 1394–1403. doi:10.1097/MOT.0b013e3282fc2633

[7] Mazzaferro V, Llovet JM, Miceli R et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Mi-

lan criteria: a retrospective, exploratory analysis. Lancet Oncol 2009; 10 (1): 35–43

[8] Duvoux C, Roudot-Thoraval F, Decaens T et al. Liver transplantation for hepatocellular carcinoma: a model including alpha-fetoprotein improves the performance of Milan criteria. Gastroenterology 2012; 143 (4): 986–994 e3. doi:10.1053/j.gastro.2012.05.052

[9] Organ Procurement and Transplantation Network. Guidance to Liver Transplant Programs and the National Liver Review Board for: Adult MELD Exceptions for Hepatocellular Carcinoma (HCC). 2023. https://optn.transplant.hrsa.gov/media/gqlnhrtn/20200804_nlrb_adult_hcc_guidance.pdf

[10] Reig M, Forner A, Rimola J et al. BCLC strategy for prognosis prediction and treatment recommendation: The 2022 update. Journal of Hepatology 2022; 76 (3): 681–693. doi:10.1016/j.jhep.2021.11.018

[11] Llovet J, Brú C, Bruix J. Prognosis of Hepatocellular Carcinoma: The BCLC Staging Classification. Semin Liver Dis 1999; 19 (3): 329–338. doi:10.1055/s-2007-1007122

[12] Matsumoto MM, Mouli S, Saxena P et al. Comparing Real World, Personalized, Multidisciplinary Tumor Board Recommendations with BCLC Algorithm: 321-Patient Analysis. Cardiovasc Intervent Radiol 2021; 44 (7): 1070–1080

[13] Lai Q, Lesari S, Lerut JP. The impact of biological features for a better prediction of posttransplant hepatocellular cancer recurrence. Current Opinion in Organ Transplantation 2022; 27 (4): 305–311. doi:10.1097/MOT.0000000000000955

[14] Gundlach JP, Schmidt S, Bernsmeier A et al. Indication of Liver Transplantation for Hepatocellular Carcinoma Should Be Reconsidered in Case of Microvascular Invasion and Multilocular Tumor Occurrence. J Clin Med 2021; 10 (6): 1155. doi:10.3390/jcm10061155.

[15] Yao LQ, Chen ZL, Feng ZH et al. Clinical Features of Recurrence After Hepatic Resection for Early-Stage Hepatocellular Carcinoma and Long-Term Survival Outcomes of Patients with Recurrence: A Multi-institutional Analysis. Ann Surg Oncol 2022; 29 (7): 4291–4303

[16] Ferrer-Fàbrega J, Forner A, Liccioni A et al. Prospective validation of ab initio liver transplantation in hepatocellular carcinoma upon detection of risk factors for recurrence after resection. Hepatology 2016; 63 (3): 839–849

[17] Mehta N, Bhangui P, Yao FY et al. Liver Transplantation for Hepatocellular Carcinoma. Working Group Report from the ILTS Transplant Oncology Consensus Conference. Transplantation 2020; 104 (6): 1136–1142

[18] Sapisochin G, Castells L, Dopazo C et al. Single HCC in cirrhotic patients: liver resection or liver transplantation? Long-term outcome according to an intention-to-treat basis. Ann Surg Oncol 2013; 20 (4): 1194–1202. doi:10.1245/s10434-012-2655-1

[19] Di Sandro S, Sposito C, Ravaioli M et al. Surgical Treatment of Hepatocellular Carcinoma: Multicenter Competing-risk Analysis of Tumor-related Death Following Liver Resection and Transplantation Under an Intention-to-treat Perspective. Transplantation 2023; 107 (9): 1965–1975. doi:10.1097/TP.0000000000004593