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Extended criteria for liver transplantation in hepatocellular carcinoma. A retrospective, multicentric validation study in Belgium

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ABSTRACT

Background: Recent studies indicate that a group of patients with cirrhosis receiving a liver transplantation for hepatocellular cancer (HCC) beyond the Milan Criteria (MC) can achieve a similar outcome compared to patients within these criteria. This study aims to investigate the value of the Asan critera (AC), up-to-7 criteria (UT7), French alpha-foetoprotein (AFP) model and Metroticket 2.0 (MT2.0) model compared to the MC.

Methods: 526 patients transplanted for non-metastatic HCC were analyzed. Patient groups within and beyond MC and extended criteria were determined according to radiological assessment and AFP value at listing.

Results: Overall survival (OS) and recurrence (RR) rates were similar between patients within MC and all extended criteria. Five-year OS within MC was 71.3% compared to 70.9% for AC, 71.4% for UT7, 69.7% for AFP-model and 71.0% for MT2.0 criteria. Five-year RR within MC was 12.3% compared to 13.5% for AC, 13.0% for UT7, 14.3% for AFP-model and 13.2% for MT2.0 criteria. Patients beyond MC but within the extended criteria had tendency towards higher recurrence.

Conclusions: All validated extended criteria (AC, UT7, AFP-model and MT2.0) could be proposed as alternatives to the MC with similar outcome. Prospective data are awaited to assess recurrence beyond MC.

1. Introduction

In the Eurotransplant (ET) countries the gold standard for liver transplantation (LT) in patients with hepatocellular cancer (HCC) are the Milan Criteria (MC). These criteria are derived from a prospective study published in 1996 by Mazzaferro et al. which studied 48 patients with cirrhosis and small, non resectable HCC [1]. Using these criteria (1 lesion less than 5 cm or up to 3 lesions each not exceeding 3 cm at imaging, in absence of macrovascular invasion and extrahepatic metastases) results in a four-year overall and disease-free survival rates of 75% and 83% respectively [1,2] which is comparable to LT in cirrhotic patients not transplanted for cancer. The MC have been validated in multiple studies [2,3]. In recent years however, the MC have been challenged because similar post-transplant overall survival (OS) and recurrence rate (RR) could be achieved with extended criteria in mostly

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retrospective cohorts. Furthermore approximately 25% of the patients classified as within MC before LT were beyond MC in the explant histology. [2] The MC are being considered too strict, excluding unjustified specific subgroups who could benefit from LT. Different extended criteria were proposed based on morphometric criteria (e.g. the Asan Medical Centre criteria (AC), up-to-seven criteria (UT7) or University of California San Francisco criteria [4]) or adding a marker of biological behavior such as alpha-foetoprotein (AFP) in the French model, Metroticket 2.0 model (MT2) or Hangzhou criteria [5] (list is not exhaustive).

List of abbreviations

AC	Asan Medical Centre criteria
AFP	Alpha-foetoprotein
HCC	Hepatocellular carcinoma
LT	Liver transplantation
MC	Milan criteria
MT2.0	Metroticket 2.0 model
OS	Overall survival
RR	Recurrence rate
UT7	Up-to-7 criteria

Table 1
Patient characteristics.

Demographic characteristics	Mean ± standard deviation
Gender	407 (77.4%) male/119 (22.6%) female
Age (yr)	58.7 ± 8.1
Underlying disease	
Hepatitis B	50 (9.5%)
Hepatitis C	167 (31.7%)
Alcoholic liver disease	226 (43.0%)
NAFLD	33 (6.3%)
Pre-transplant characteristics	
MELD	11.4 ± 4.2
Waiting time from listing (months)	5.7 ± 5.7
Tumor control therapy on list	279 (53.0%)
AFP (ng/ml) at listing	99.9 ± 539.4
Radiological characteristics at listing	
Number of lesions	1.5 ± 1.8
Size of largest nodule (cm)	2.1 ± 1.9
Radiological characteristics at transplant	
Number of lesions	1.8 ± 1.7
Size of largest nodule (cm)	2.5 ± 1.9
Pathological characteristics explant	
Number of lesions	2.9 ± 5.2
Size of largest nodule (cm)	2.1 ± 2.0
Tumor differentiation (poor/undifferentiated)	33 (6.3%)
Macrovascular invasion	15 (2.9%)
Microvascular invasion	156 (29.7%)

The extended AC allow patients with up to 6 HCC nodules eligible for transplantation. The largest tumor diameter remains ≤5 cm, and there may be no gross vascular invasion. These criteria are based on a single-center study including 221 patients with HCC who underwent living donor LT. The 5-year OS was 76.3% and 18.9% within and beyond the AC. There was a 3-year RR of 9.1% in patients exceeding the MC but within the AC. The AC have been validated in non-living donor LT in western countries [6–8].

In 2009 Mazzaferro et al. proposed the UT7 criteria as the result of a multicenter retrospective European study with seven being the maximal allowed sum of the size of the largest tumor (in cm) and the number of tumors for any given HCC (if microvascular invasion was absent). The 5-year OS in this group of 283 patients was 71.2%, which was not significantly different from patients within the MC. The 5-year RR for patients within the UT7 criteria was 9.1% [9]. Recently the MT2.0 model was published incorporating AFP in the UT7 criteria [10]. For patients with HCC to have a 70% chance of HCC-specific survival 5 years after transplantation, their level of AFP should be < 200 ng/mL and the sum of number and size of tumors should not exceed 7; if the level of AFP was 200–400 ng/mL, the sum of the number and size of tumors should be ≤ 5 and if their level of AFP was 400–1000 ng/mL, the sum of the number and size of tumors should be ≤ 4.

Another promising model based on AFP, published by Duvoux et al. [11] has been implemented in France. According to this AFP-model patients with 1–3 tumors and a largest tumor diameter of 6 cm, or with ≤4 lesions with a maximal diameter of 3 cm are considered eligible for transplantation if their AFP level is ≤ 100 ng/mL. Among patients within MC, the model identified a subgroup of patients with AFP values greater than 1000 ng/mL at high risk of recurrence and reduced survival.

In this retrospective, multicentric study the aim was to further investigate the value of the Asan criteria (AC), the up-to-7 criteria (UT7), the AFP-model (AFP) and the metroticket 2.0 model (MT2.0) as recently validated extended scoring systems, compared to the MC as gold standard. For this purpose we evaluated the overall survival (OS) and recurrence rate (RR) of patients within and beyond the MC and extended criteria. The groups were defined at listing as this best reflects clinical practice. We also compared the outcome of the subgroup of patients beyond the MC, but within the extended criteria. Secondly, we defined the same groups according to the available data at transplantation to address the possible influence of bridging therapy during waiting time on our results.

2. Patients and methods

2.1. Patients

714 adult patients with a pre-operative radiological diagnosis of non-metastatic HCC who were listed for LT from 1999 to 2016 were included in this retrospective multicentric Be-LIAC study. Due to missing data, 526 patients were finally analyzed at listing and 203 patients at transplantation.

Patients were enrolled from the 6 different transplant centers in Belgium. Forty-four percent (n = 233) of patients were transplanted at the Catholic University of Louvain, 20.9% (n = 110) at University Hospital Leuven, 17.3% (n = 91) at Ghent University Hospital, 10.5% (n = 55) at Erasme Hospital Free University of Brussels, 4.2% (n = 22) at University Hospital of Liège and 2.9% (n = 15) at University Hospital of Antwerp.

The mean age at liver transplantation (LT) was 58.7 years. 77.4% of patients were male, 22.6% female The most common underlying chronic liver diseases were alcoholic liver disease (43.0% of patients), hepatitis C (31.7%), hepatitis B (9.5%) and non-alcoholic fatty liver disease (6.3). The mean lab-MELD score at listing was 11.4 (SD: ±4.2). The mean time

Table 2
Number of patients beyond and within MC or extended criteria at listing. Number of events (death and recurrence)/subgroup. P-value OS and RR between patients beyond and within MC and extended criteria.

At listing	Number OUT/IN	Events (death) OUT/IN	p-value OS	Events (recurrence) OUT/IN	p-value RR
MC	90/436	41/146	0.004	28/49	<0.001
AC	41/485	25/162	<0.001	18/59	<0.001
UT7	44/482	27/160	<0.001	20/57	<0.001
AFP	47/479	22/165	0.049	15/62	<0.001
MT2.0	58/468	31/156	0.001	21/56	<0.001

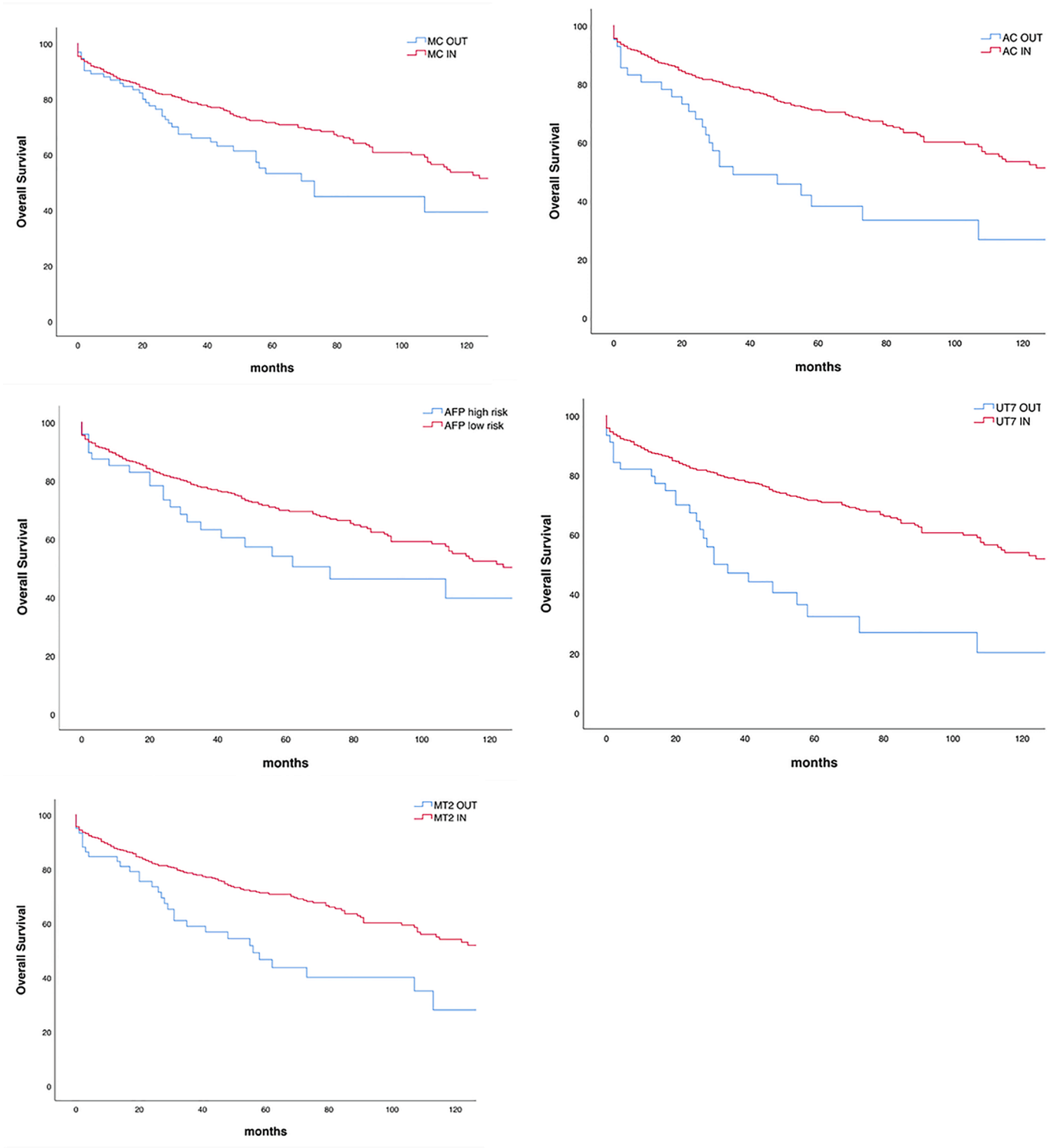

Fig. 1. Kaplan Meier curves for overall survival beyond and within MC or extended criteria.

on the waiting list until LT was 5.7 (SD: ±5.7) months. Fifty-three percent of patients received bridging therapy (n = 279, missing data: 14.8%) and 15.0% were downstaged (n = 79, missing data: 44.1%). Mean follow-up after LT was 56.1 months (SD: ±43.7) (Table 1).

2.2. Data collection

The data were retrospectively collected by 5 investigators (HD, EC, IS, IS, JS). The dataset consisted of demographic parameters, underlying

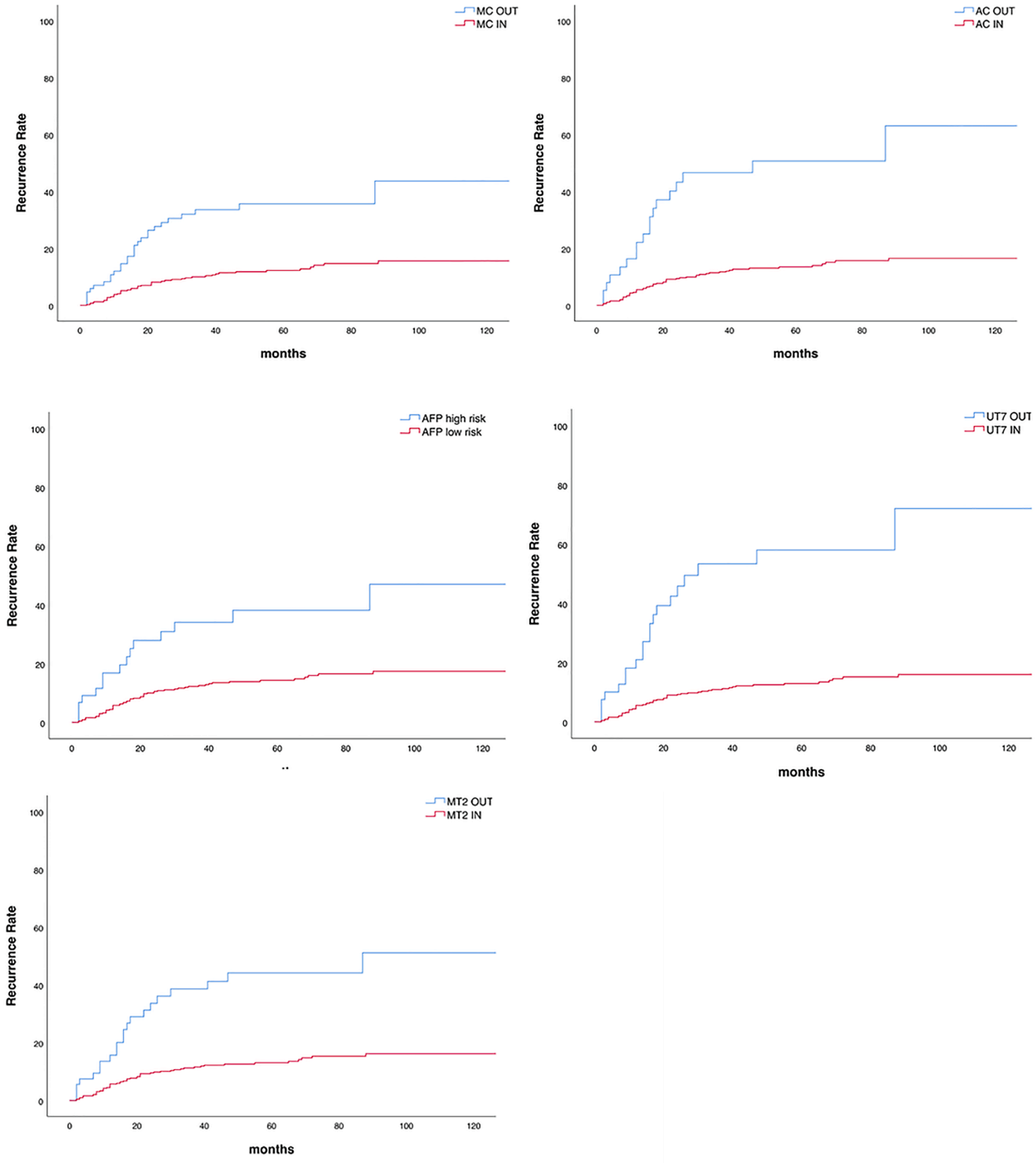

Fig. 2. Kaplan Meier curves for recurrence rate beyond and within MC or extended criteria.

Table 3
1-,3-,5- and 10-year OS and RR for patients within MC or extended criteria at listing.

At listing	1-year OS	3-year OS	5-year OS	10-year OS	1-year RR	3-year RR	5-year RR	10-year RR
MC IN	88.0%	78.5%	71.3%	53.5%	4.1%	10.0%	12.3%	15.6%
AC IN	88.4%	78.7%	70.9%	53.2%	4.6%	11.4%	13.5%	16.5%
UT7 IN	88.3%	78.9%	71.4%	53.7%	4.4%	10.9%	13.0%	16.0%
AFP IN	88.0%	77.6%	69.7%	52.2%	4.4%	12.3%	14.3%	17.4%
MT2.0 IN	88.2%	78.4%	71.0%	54.0%	4.5%	11.3%	13.1%	16.2%

Table 4
Number of patients beyond MC and within extended criteria at listing. Number of events (death and recurrence)/subgroup.

At listing	Number	Events (death)	Events (recurrence)
MC OUT + AC IN	49	16	10
MC OUT + UT7 IN	46	14	8
MC OUT + AFP IN	60	23	13
MC OUT + MT2.0 IN	44	13	8

chronic liver disease, Child Turcotte Pugh score and lab-MELD at listing, time and treatment on the waiting list.

Patient groups were determined according to radiological, pre-operative MC and extended criteria at listing and transplantation. The AFP level was also considered at listing and transplantation. Time of death and/or recurrence were recorded.

2.3. Statistical analysis

Statistical analysis was performed using SPSS statistics 23. Survival- and recurrence-rates were evaluated using Kaplan-Meier curves and groups were compared using a log-rank test. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Overall survival and recurrence rate for patients within and beyond the MC and extended criteria

At listing 17.1% of patients were beyond MC. For the extended criteria 7.8%, 8.3%, 8.9% and 11% of patients were beyond AC, UT7, AFP-model and MT2.0 criteria respectively. There was a significant higher OS and lower RR in the group of patients within MC compared to patients beyond MC ($p < 0.05$). These results were also seen for all extended criteria ($p < 0.05$) (Table 2).

The 1-,3-,5-, and 10-year OS and RR between the subgroup of patients within MC or within the extended criteria were found to be similar (Figs. 1 and 2). The 5-year OS for patients within MC was 71.3% compared to 70.9% for AC, 71.4% for UT7, 69.7% for AFP-model and 71.0% for MT2.0 criteria. All criteria showed an 10-year OS of more than 50%. The 5-year RR for patients within MC was 12.3% and for the extended criteria: 13.5% for the AC, 13.0% for UT7, 14.3% for AFP-model and 13.1% for MT2.0 criteria (Table 3).

At transplantation 27.0% of patients were beyond MC. For the extended criteria 6.4%, 11.8%, 15.3% and 16.7% of patients were beyond AC, UT7, AFP-model and MT2.0 criteria respectively (Table 6). The 5-year OS for patients within MC was 73.7% compared to 73.9% for AC, 74.9% for UT7, 75.0% for AFP-model and 75.2% for MT2.0 criteria. The 5-year RR for patients within MC was 11.4% and for the extended criteria: 12.7% for the AC, 12.2% for UT7, 13.1% for AFP-model and 11.9% for MT2.0 criteria (Table 7).

Table 5
1-,3-,5- and 10-year OS and 1-and 3-year RR for patients beyond MC and within extended criteria at listing.

At listing	1-year OS	3-year OS	5-year OS	10-year OS	1-year RR	3-year RR
MC OUT + AC IN	91.8%	80.9%	66.9%	55.2%	8.6%	23.7%
MC OUT + UT7 IN	91.2%	82.2%	71.5%	60.8%	6.8%	18.8%
MC OUT + AFP IN	88.3%	72.8%	61.0%	51.9%	5.3%	24.2%
MC OUT + MT2.0 IN	90.9%	81.8%	74.7%	63.3%	7.0%	19.3%

Table 6
Number of patients beyond and within MC or extended criteria at transplantation. Number of events (death and recurrence)/subgroup.

At transplant	Number OUT/IN	Events (death) OUT/IN	Events (recurrence) OUT/IN
MC	55/148	20/37	12/13
AC	13/190	7/50	6/19
UT7	24/179	12/45	8/17
AFP	31/172	13/44	7/18
MT2.0	34/169	14/43	9/16

3.2. Overall survival and recurrence rate for patients beyond MC but within extended criteria

Subgroup analysis compared patients within MC versus patients beyond MC but still within the extended criteria. At listing the 5-year OS for patients beyond MC, but within AC was 66.9%, 71.5% for UT7, 61.0% for AFP-model and 74.8% for MT2.0 criteria. All extended criteria achieved an 10-year OS of more than 50%. The 3-year RR was 23,7%, 18.8%, 24.2% and 19.3% for the AC, UT7, AFP-model and MT2.0 criteria respectively. All recurrences occurred within the first 3-years of follow-up (Tables 3–5, Fig. 3) (See. Table 8)

At transplantation the 5-year OS for patients beyond MC, but within AC was 75.0%, 77.5% for UT7, 82.6% for AFP-model and 84.4% for MT2.0 criteria. The 3-year RR was 13,9%, 11.1%, 18.3% and 12.5% for the AC, UT7, AFP-model and MT2.0 criteria respectively (Table 9).

4. Discussion

In this validation study the use of extended criteria for selecting patients with HCC in liver cirrhosis for LT was investigated by comparison with the MC as 'gold standard'. Since Mazzaferro's study in 1996, many attempts have been made to expand (and improve) these criteria. Several authors have described modest expansions of the MC in size and/or number of HCC lesions on imaging or explant, with acceptable OS and RR. Tumor differentiation and vascular invasion are also predictors of outcome after LT, but only available after pathologic examination of the specimen. Therefore surrogate markers reflecting tumor biology such as Alpha-foetoprotein (AFP) [11–13] are likely to become more important in future allocation systems. Furthermore, dynamic variables for example the waiting time on the transplant list, radiological response after locoregional therapy and the evolution in AFP on the waiting list are currently being explored [14–17].

Until now there is no uniformity concerning the most valid alternative allocation system. It is a fact however, that an increasing percentage of patients with HCC undergoes transplantation beyond conventional indications. Recently, the use of (non-specified) extended criteria has also been cited in international guidelines which leads to non-uniformed allocation protocols between different centers [18,19]. Consequently validation of extended criteria is an important and urgent need.

In the studied Be-LIAC cohort the OS was 64.4% (n = 339/526) and the RR 14.6% (n = 77/526) during a mean follow-up after LT of 56.1 months (SD: ±43.7). Patients within MC had a 5-year OS of 71.3% and 5-year RR of 12.3%. At listing 17.1% of patients were beyond MC. There

Table 7
1-,3- and 5-year OS and RR for patients within MC or extended criteria at transplantation.

At transplant	1-year OS	3-year OS	5-year OS	1-year RR	3-year RR	5-year RR
MC IN	89.7%	80.9%	73.7%	3.7%	10.1%	11.4%
AC IN	89.2%	81.2%	73.9%	3.4%	10.9%	12.7%
UT7 IN	90.3%	81.9%	74.9%	3.0%	10.3%	12.2%
AFP IN	90.5%	81.2%	75.0%	3.8%	12.1%	13.1%
MT2.0 IN	90.4%	81.4%	75.2%	3.2%	10.9%	11.9%

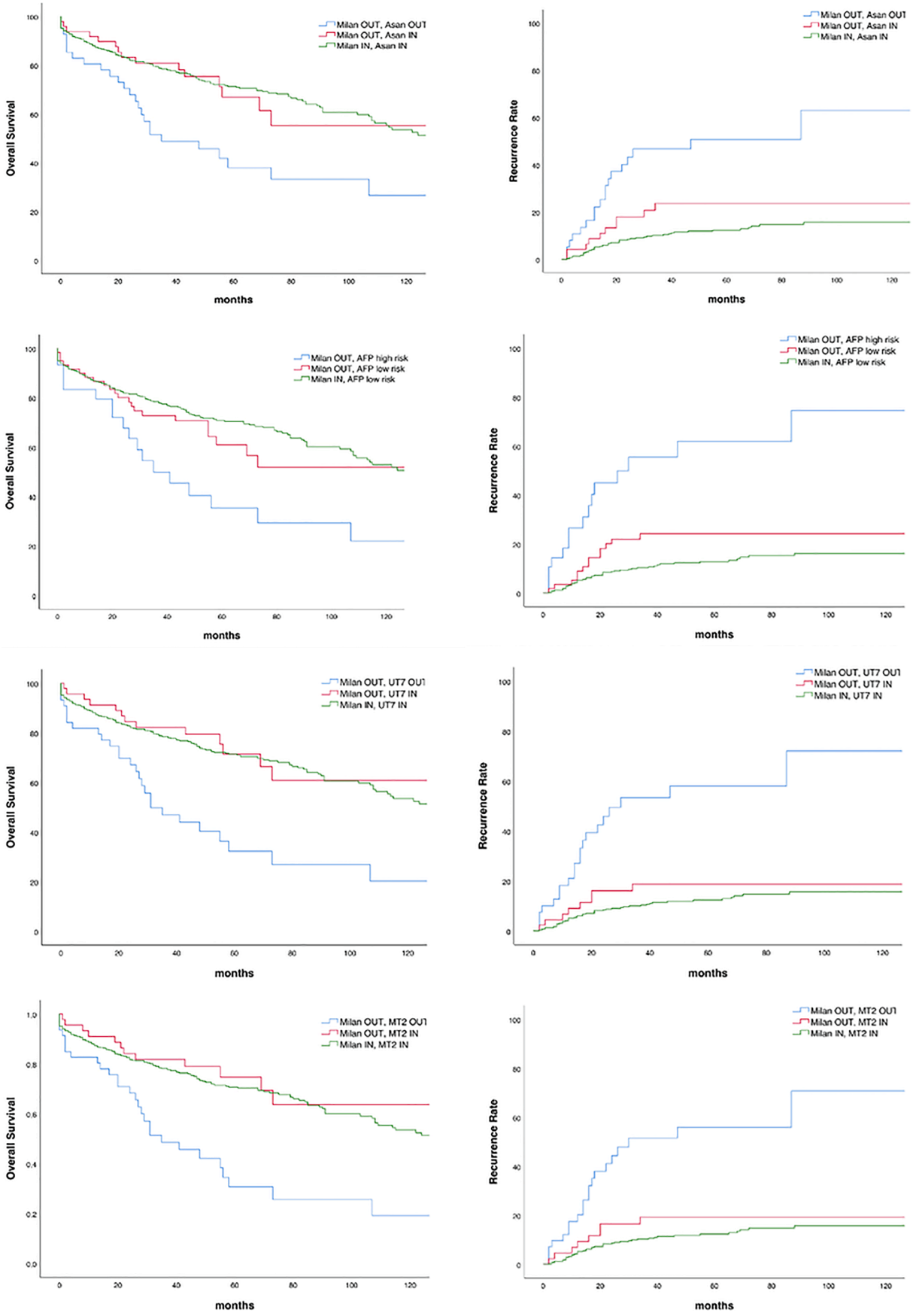

Fig. 3. Kaplan Meier curves for overall survival and recurrence rate beyond MC and within extended criteria.

Table 8
Number of patients beyond MC and within extended criteria at transplantation. Number of events (death and recurrence)/subgroup.

At transplant	Number	Events (death)	Events (recurrence)
MC OUT + AC IN	42	13	6
MC OUT + UT7 IN	32	9	4
MC OUT + AFP IN	30	8	5
MC OUT + MT2.0 IN	27	7	3

Table 9
1-, 3- and 5-year OS and 1-, 3- and 5-year RR for patients beyond MC and within extended criteria at transplantation.

At transplant	1-year OS	3-year OS	5-year OS	1-year RR	3-year RR	5-year RR
MC OUT + AC IN	92.7%	82.4%	75.0%	2.4%	13.9%	17.4%
MC OUT + UT7 IN	93.5%	83.5%	77.5%	0%	11.1%	15.6%
MC OUT + AFP IN	96.6%	82.6%	82.6%	3.4%	18.3%	
MC OUT + MT2.0 IN	96.2%	84.4%	84.4%	0%	12.5%	

was a significant higher OS and lower RR in the group of patients within MC compared to patients beyond MC ($p < 0.05$). These results were also seen for the different groups of patients within each studied extended criteria compared to patients beyond the criteria ($p < 0.05$). Moreover the 1-,3-,5-, and 10-year OS and RR between patients within MC or the extended criteria were found to be similar. These results could be strengthened with similar findings at transplantation, taking into account the possible influence of bridging therapy during waiting time. Altogether the results suggest that all extended criteria can be used as an alternative for the MC. To our knowledge this is also the first large, multicentric study that can retrospectively validate the recently published MT2.0 model.

However our results must be interpreted with caution. Comparing patients within and beyond the extended criteria is not sufficient, because of a dilution effect of all the included patients within the MC. Subgroup analysis showed that patients beyond MC but within all the extended criteria had a tendency towards higher RR. This finding reflects the Metroticket paradigm introduced by Mazzaferro et al., in 2009, stating that the further the distance from conventional limits, the higher the price in terms of malignant recurrences [3,20]. On the other hand the 5-year OS for the subgroup of patients beyond MC but within the extended criteria was more than 50%. All the criteria met the 5-year patient survival rate of at least 61% required for an allocation system to be seen as ethically acceptable comparing the survival benefit of LT for a patient beyond the MC and the harm caused to other patients on the waiting list. However, this calculation is related to the waiting time and characteristics of donation [21]. The small number of patients and events (death as well as recurrence) in this subgroup of our cohort is too limited for reliable statistical analysis or definite conclusions. The statistical analysis was also not powered to show equivalence between the MC and the extended criteria.

Another remark is the limited number of patients at the utter limits of the extended criteria. In the studied cohort the mean diameter of the largest lesion in the subgroup beyond MC but within extended criteria was 3.3 (±SD: 1.0) for AC, 3.5 (±SD: 1.3) for UT7, 3.4 (±SD: 1.4) for AFP-model and 3.5 (±SD: 1.3) for MT2.0 criteria. This might have given an overestimation of the good performance of the extended criteria.

Considering the time point of listing for liver transplantation to validate allocation criteria best reflects clinical practice and decision making. However during the waiting time (5.7 ± 6.4 months) lesions might have been falsely underestimated due to tumor growth. On the other hand many patients (53.0%) received bridging therapy which might have overestimated lesions at listing in case of tumor shrinkage. For this reason we secondly analyzed the same groups at the nearest time point before transplantation and found similar results. The main problem with this last approach is that in daily practice standardized imaging is not performed exactly at the time of transplantation, resulting for this retrospective study in missing or less accurate data with smaller subgroups and fewer events.

When extending criteria the availability of donor organs should be taken into account. The amount of extra eligible patients for LT would be 10.1% when using AC, 9.5% for UT7, 12.5% for the AFP-model and 9.4% for the MT2.0 models. A limitation to this estimation is the inclusion of only transplanted patients in this study. A potentially substantial group of patients that are beyond MC but within extended criteria have never been transplanted and were not taken into account. For the same reason we have no data about the dropout rate on the waiting list.

Finally, extending criteria should not be the only field that merit attention. Other options to optimize patient survival and reduce the RR after LT should be looked at such as pre-operative imaging techniques using PET-CT scan [22], the use of mTOR inhibitors [23–25] as immunosuppressive regimen and most importantly the benefit of locoregional therapies with the proper assessment and timing of response [26–28]. In this regard the latest EASL Clinical Practice Guidelines (2018) state that LT for patients beyond MC can be considered after successful downstaging to within MC within defined protocols [17].

Altogether this study again urges the ongoing debate whether it is still too early to expand beyond the MC. In the variety of published criteria there is not yet a consensus on which parameters to use. It is likely that current proposals will need modifications in the next years and that boundaries will be pushed further in every new trial. For example the extended Toronto criteria include patients with any size or number of tumors for transplantation (since 2004) provided they do not have systemic cancer-related symptoms, extrahepatic disease, vascular invasion, or poorly differentiated tumors on tumor biopsy of the largest lesion [29]. We are limited by the fact that current knowledge is almost completely based on retrospective validation studies. Prospective data from centers already using extended criteria in real life are still awaited. On the other hand, by using the MC, we might deny good candidates for transplantation a possible curative treatment. It is of utmost importance not to miss an opportunity to uniform the used allocation criteria.

5. Conclusion

In this Be-LIAC multicenter study similar overall survival and recurrence rate were observed in patients within MC and all extended criteria (AC, UT7, AFP-model and MT2.0). Therefore these criteria could be considered as alternative selection criteria for liver transplantation in HCC patients with an underlying liver disease. Prospective studies are warranted as an increased recurrence rate in the subgroup of patients beyond MC has been observed in this cohort.

Authorship

HD, EC, IS, JD, JS: data acquisition, HD, EC, IS, JD: designed the research and wrote the manuscript, all authors: read, edited the manuscript and approved the final manuscript.

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Declaration of competing interest

No conflict of interest reported in relation to the presented work.

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