HEPATOLOGY

HEPATOLOGY, VOL. 66, NO. 6, 2017

Intention-to-Treat Survival Benefit of Liver Transplantation in Patients With Hepatocellular Cancer

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The debate about the best approach to select patients with hepatocellular cancer (HCC) waiting for liver transplantation (LT) is still ongoing. This study aims to identify the best variables allowing to discriminate between "high-" and "low-benefit" patients. To do so, the concept of intention-to-treat (ITT) survival benefit of LT has been created. Data of 2,103 adult HCC patients consecutively enlisted during the period 1987-2015 were analyzed. Three rigorous statistical steps were used in order to create the ITT survival benefit of LT: the development of an ITT LT and a non-LT survival model, and the individual prediction of the ITT survival benefit of LT defined as the difference between the median ITT survival with (based on the first model) and without LT (based on the second model) calculated for each enrolled patient. Four variables (Model for End-Stage Liver Disease, alpha-fetoprotein, Milan-Criteria status, and radiological response) displayed a high effect in terms of delta benefit. According to these risk factors, four benefit groups were identified. Patients with three to four factors ("no-benefit group"; n = 405 of 2,103; 19.2%) had no benefit of LT compared to alternative treatments. Conversely, patients without any risk factor ("large-benefit group"; n = 108; 5.1%) yielded the highest benefit from LT reaching 60 months. *Conclusion:* The ITT transplant survival benefit presented here allows physicians to better select HCC patients waiting for LT. The obtained stratification may lead to an improved and more equitable method of organ allocation. Patients without benefit should be de-listed, whereas patients with large benefit ratio should be prioritized for LT. (HEPATOLOGY 2017;66:1910-1919).

The debate about the best approach for selecting patients with hepatocellular cancer (HCC) waiting for liver transplantation (LT) is still ongoing. Recent literature has shown that outcome of HCC patients in which the selection for LT is based on specific restrictive tumor characteristics may generate survival rates comparable to those obtained post-LT in non-HCC patients. Furthermore, LT may also represent an optimal treatment for HCC patients harboring tumors being out of conventional (Milan) criteria if morphological and biological tumor behavior is taken into account.[(1)] Consequently, the line between the need to justifiably transplant as many patients as possible and the necessity to select only patients having

Abbreviations: AIC, Akaike information criterion; AFP, alpha-fetoprotein; CR, complete response; DO, drop-out; EurHeCaLT, European Hepatocellular Cancer And Liver Transplantation; FU, follow-up; HCC, hepatocellular cancer; IQR, interquartile range; ITT, intention-to-treat; LRT, locoregional treatment; LT, liver transplantation; MC, Milan criteria; MELD, Model for End-Stage Liver Disease; MESIAH, Model to Estimate the Survival In Ambulatory patients with HCC; mRECIST, modified Response Evaluation Criteria in Solid Tumors; PR, partial response; PD, progression disease; SD, stable disease; WL, waiting list; WT, waiting time.

Received November 17, 2016; accepted June 23, 2017.

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.29342/suppinfo.

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DOI 10.1002/hep.29342

Potential conflict of interest: Dr. Cillo advises for Roche, Pfizer, and Novartis. Dr. Lerut is on the speakers' bureau for Astellas.

an effective benefit from LT is very thin and represents therefore an everyday clinical challenge.

Recently, the concept of "transplant benefit," corresponding to the number of years gained by LT minus the number of years offered by alternative treatments, has been proposed in the field of LT.[2] In the context of non-HCC patients, the concept of transplant benefit has been efficaciously adopted. Indeed, patients with a Model for End-Stage Liver Disease (MELD) score <15 do not improve their survival if transplanted or if staying on the waiting list (WL).[2] When follow-up period is no longer than 10 years, transplant benefit estimation is equally influenced by pre-LT and post-LT variables, thus providing a balance between the concepts of pure urgency ("the sickest first") and pure utility (the highest survival gain).[3]

However, the definitive answer on the best pre-LT and post-LT variables to be used for selecting HCC patients able to reach an effective benefit from LT is still needed. Apart from morphological aspects, biological and "time-dependent" variables have been recently added in the LT selection process.[4] Among them, waiting time (WT), alpha-fetoprotein (AFP) values, and radiological response after neoadjuvant locoregional treatment (LRT) have been largely explored.[5-9]

Moreover, transplant benefit values have been always evaluated from the moment of LT and not from the moment of WL inclusion. In the present study, the innovative concept of intention-to-treat (ITT) transplant benefit has been proposed. ITT survival is defined as the LT survival from the moment of patient enlistment and not from the day of LT,[10] having been widely accepted in the LT community.[11,12] The use of an ITT survival analysis allows the opportunity to analyze the results based on the initial treatment assignment and not on the treatment eventually received, thus avoiding various misleading artifacts and initial selection biases.

The aim of the present study is then to analyze a large, multicenter European collaborative project, with the intent to identify the best variables able to discriminate high- or low-benefit patients. In order to do so, an ITT survival benefit has been developed, aiming at identifying different patient subgroups deserving or not LT.

Materials and Methods

A retrospective analysis of data from 2,103 adult (aged ≥18 years) patients with radiological and/or pathological diagnosis of HCC was performed. All patients were listed for LT during the period from January 1, 1987 to December 31, 2015 and being dropped-out or undergoing a first LT during the same time period. Data were obtained from the prospectively collected databases of 10 collaborative European Centers involved in the EURopean HEpatocellular CAncer and Liver Transplantation (EurHeCaLT) Project. The participating centers were Padua, Italy (n = 346); Brussels, Belgium (n = 336); Innsbruck, Austria (n = 330); Sapienza University, Rome, Italy (n = 243);

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Royal Free, London, UK (n = 193); Mainz, Germany (n = 176); San Camillo Hospital, Rome, Italy (n = 142); Tor Vergata University, Rome, Italy (n = 140); Ancona, Italy (n = 110); and Catholic University, Rome, Italy (n = 87).

Patients with incidental tumors, mixed hepatocellular-cholangiocellular tumors, or cholangiocellular cancer misdiagnosed as HCC were excluded from the analysis.

Of note is that all of the participating centers do not consider any longer Milan criteria (MC) as the limit for inscription on the WL: consequently, 636 (30.2%) MC-OUT patients were enlisted. Despite that different policies were used in the different centers, all the transplanted cases reported on were within University of San Francisco California criteria, up-to-seven criteria, or Tokyo ("5+10 role") criteria: so, the dimensional upper limit observed in the present study was 6.5 cm of diameter in the target lesion and 10 nodules. A majority of patients (n = 1,754; 83.4%) had pre-LT multimodal LRT. Such a policy allowed an in-depth analysis of the response to LRT as a possible selection variable. All analyzed patients were categorized in different groups according to the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria termed as complete response (CR), partial response (PR), stable disease (SD), and progression disease (PD).[10] Patients which did not have LRT were considered as the no-LRT group: The decision to not consider no-LRT patients with a possible increase of the tumor burden before LT into the PD group derived from the consideration that these patients do not fully correspond from a biological point of view to patients with a tumor with a PD after a radiological treatment. In the treated patients, mRECIST status was defined after comparison between initial imaging at WL inscription and the last available one before LT or drop-out (DO).

Patients listed before 1996 and 2010 were reclassified according to MC and mRECIST criteria according to the retrospective evaluation of their imagings.[1,13]

The adopted cutoffs of 1,000 ng/mL and 15 ng/mL/month for AFP and AFP slope were selected according to literature data.[6,7] The AFP slope was calculated using the two values at the moment of WL inscription and the one immediately before LT or DO. The adopted WT cutoff of 120 days and MELD cutoff of 13 were also chosen according to previous reports.[5,11,14]

Median patient follow-up (FU) from the moment of WL inscription was 3.7 years (interquartile range [IQR], 1.4-7.6).

STATISTICAL ANALYSIS

Continuous variables were reported as medians and IQR. Dummy variables were reported as numbers and percentages. Missing data relative to study covariates always involved less than 10% of patients. Thus, they were estimated using the maximum likelihood estimation method.[15]

The statistical design of this study included three main steps: (1) the development of an ITT LT survival model; (2) the development of a non-LT survival model and; (3) the individual prediction of the ITT survival benefit of LT defined as the difference between the median ITT survival with LT (based on the first model) and median survival without LT (based on the second model) calculated for each enrolled patient. The specific steps for the construction of the models are diffusely explained in Supporting Data S1. We briefly reported here the statistical steps we adopted.

First, the ITT LT survival model was constructed using a log-logistic model: the results of the model are reported in Supporting Table S1. The obtained results of the model were applied to predict ITT median survival with LT of each enrolled patient.

Non-LT survival model was built starting from some assumptions: the majority of WL patients are censored by LT[16,17]; median WT of HCC patients is relatively short, thus prediction of long-term survival of these patients may be inaccurate.[5] Several statistical techniques have been proposed for resolving this problem.[16-18] However, these methods are still insufficient to resolve the biases related to the complexity of WL dynamics, often requiring arbitrary corrections.[18,19] The Model to Estimate the Survival In Ambulatory patients with HCC (MESIAH) was then adopted for resolving this problem.[14] This model, recently validated both in Western and Eastern countries,[20,21] provides a simple formula to translate the MESIAH score in individual survival predictions. Using patient characteristics at the last evaluation before LT or DO, we used the MESIAH score to simulate the median time to death that patients censored by LT would have had in the absence of LT. This simulated time to death was therefore used to perform a second log-logistic parametric survival model to find significant predictors of non-LT survival: The results of the model are reported in Supporting Table S2. Then, we used this second model to predict non-LT median survival of each enrolled patient.

Finally, The ITT LT and the non-LT survival log-logistic models generated two median survival predictions

for each enrolled patient. The ITT survival benefit of LT was therefore calculated for each patient as the difference between ITT LT median and the non-LT median survival estimations. All estimations were capped at 120 months, because this time horizon represents the ideal balance between utility and urgency allocation principles.[4] A multivariate least square regression was finally used to find significant predictors of ITT LT benefit among studied variables.[22,23] In all the multivariable survival models, all variables with $P < 0.1$ at the univariate model were included. In the final model, only variables showing a significant impact on survival at the first multivariable model were maintained.

Given that *P* values can be biased from population size, results of survival benefit estimations in covariates subgroups were reported as effect size. Effect size is a standard measure that can be calculated from any number of statistical outputs. One type of effect size, the standardized mean effect, expresses the mean difference between two groups in standard deviation units. Typically, it is reported as Cohen's *d*, or simply referred to as the *d* value.[24]

Variables with a $P < 0.05$ were considered statistically significant. The calculations were done with JMP (1989-2003; SAS Institute Inc, Cary, NC.) and Stata/IC (13.0 [1985-2013]; StataCorp LP, College Station, TX) packages.

Results

Demographics of the entire population are displayed in Table 1. Two hundred forty-six (11.7%) of 2,103 patients dropped out during the WT period: 160 of 246 (65.0%) cases dropped out because of HCC progression, with 143 of 246 (58.1%) patients dying during the WT period. Looking more in detail at the reasons of DO, 69 patients were excluded because of HCC progression (patient alive at the moment of DO). In 91 cases, a tumor-related death on WL was observed; 52 patients showed a liver-disease–related death on WL, 25 moved to another center, and 9 were excluded because of poor compliance.

A total of 1,857 patients underwent LT: 242 (13.0%) patients recurred. When considering the 1,504 patients having a minimum FU of 1 year post-LT, the recurrence rate was 16.1%.

After the construction of the different models, a multivariate least square regression analysis finally identified eight variables as significant predictors for ITT transplant benefit. Five variables favored an increase of benefit: age at listing (β-coefficient = 1.3; *P* value = 0.0006); MELD at LT or DO (β-coefficient =1.1; *P* value, <0.0001); WT duration

TABLE 1. Patient- and Tumor-Related Characteristics in the EURHECALT Study Population

Variables	Study Group (n = 2,103) Median (IQR) or n (%)
Period of WL inscription (1987-2000 vs. 2001-2015)	301/1,802 (14.3/85.7)
WT days	137 (57-284)
≥120	963 (45.8)
Male sex	1,763 (83.8)
Recipient age at WL inscription (years)	56.8 (49.7-62.0)
≥60	731 (34.8)
Cause of underlying cirrhosis*	
HCV	1,001 (47.6)
HBV	391 (18.6)
Alcohol	631 (30.0)
Laboratory MELD at LT or DO	12 (9-16)
MELD ≤13	1,395 (66.3)
Laboratory albumin (g/dL) at LT or DO	4.0 (3.8-4.0)
HCC at WL inscription	
Major lesion diameter (cm)	3.0 (2.0-4.0)
No. of lesions	2 (1-3)
MC-OUT status	636 (30.2)
Last radiological HCC assessment	
Major lesion diameter (cm)	2.0 (0.0-3.0)
No. of lesions	1 (1-3)
MC-OUT status	476 (22.6)
University of San Francisco California Criteria status	349 (16.6)
Up-to-seven Criteria status	253 (12.0)
Tokyo criteria ("5+10 role") status	114 (5.4)
LRT†	1,754 (83.4)
Total no. of procedures	2 (1-3)
Complete response	380 (18.1)
Progressive disease	491 (23.3)
AFP	
At listing (ng/mL)§	10.0 (4.8-37.3)
Last available AFP (ng/mL)	9.7 (4.4-34.9)
≥1000 ng/mL	63 (3.0)
Slope ≥15 ng/mL/month§	228 (12.6)
DO	246 (11.7)
HCC-related DO	160 (7.6)
Death during WT	143 (6.8)
Recurrence‡	242/1,504 (16.1)
Within 1 year after LT	76/1,504 (5.1)
Within 2 years after LT	138/1,504 (9.2)
Within 3 years after LT	172/1,504 (11.4)
Within 5 years after LT	213/1,504 (14.2)

*Multiple causes in the same patient: HCV + alcohol = 101; HCV + HBV = 29; HBV + alcohol = 22; HCV + HBV + alcohol = 6; alcohol + other = 6; HCV + other cause = 5; alcohol + NASH = 5; HCV + alcohol + other cause = 3; HBV + other cause = 3; HCV + HBV + alcohol + NASH = 1.
†Percentages calculated only on patients undergoing LRT.
‡Percentages calculated only on transplanted patients with FU >1 year.
§Medians, IQRs, and percentages calculated on 1,804 (85.8%) cases with available data.
Abbreviations: HCV, hepatitis C virus; HBV, hepatitis B virus; NASH, nonalcoholic steatohepatitis.

TABLE 2. Multivariate Least Square Regression Evaluating Significant Predictors of ITT Transplant Benefit

Variables	Multivariable Model: Coefficient ± SE (Months)	Multivariable Model: *P* Value
Constant	−14.7 ± 2.7	<0.0001
WL inscription before 2001	−25.3 ± 1.0	<0.0001
Age at listing (per year)/10	1.3 ± 0.4	0.0006
MELD at LT or DO	1.1 ± 0.1	<0.0001
WT (per month)	0.1 ± 0.03	0.001
mRECIST progression disease	−36.8 ± 0.9	<0.0001
Last radiological HCC assessment		
Major lesion diameter (cm)	10.9 ± 0.4	<0.0001
No. of lesions	6.5 ± 0.3	<0.0001
Last available logAFP	−3.4 ± 0.2	<0.0001

The constant term in the final model represents the estimated ITT survival benefit of LT in the mean patient. The covariates effects for the estimated ITT benefit are assumed to be additional to the constant term.

(β-coefficient = 0.1; *P* value = 0.001); last radiological HCC assessment of the major lesion diameter (β-coefficient = 10.9; *P* value, <0.0001); and of number of HCC lesions (β-coefficient = 6.5; *P* value, <0.0001). In other terms, a higher benefit was reported in older patients, if MELD or WT increased, or if greater tumors were transplanted.

Three variables pointed toward a poor benefit: WL inscription before 2001 (β-coefficient = −25·3; *P* value, <0.0001), mRECIST PD (β-coefficient = −36.8; *P* value, <0.0001), and last available logAFP value (β-coefficient = −3.4; *P* value, <0.0001). In other terms, being listed before 2001, presence of radiological PD and progressive increase in AFP values were all linked to a poor benefit (Table 2).

ITT transplant benefit estimations in different clinically relevant subgroups were also looked at (Table 3). Five variables showed a moderate-to-high effect in terms of differences of median benefit: Patients with last AFP value ≥1,000 ng/mL (6.8 vs. 25.4 months in patients with AFP <1,000 ng/mL; *d* value = 0.69), lab-MELD ≤13 (19.8 vs. 39.1 months in patients with MELD >13; *d* value = 0.81), mRECIST PD (10.6 vs. 29.2 months in patients without PD; *d* value = 0.78), and mRECIST CR (7.2 vs. 28.7 months in patients without CR; *d* value = 0.90) had very disappointing benefits. MC-IN status (22.8 vs. 34.5 months in patients exceeding MC; *d* value = 0.47) and WL inscription before 2001 (10.4 vs. 27.3 months in patients enlisted after 2001; *d* value = 0.49) presented only a moderate benefit discrimination (Table 3; Fig. 1).

Based on these results, it was first decided to exclude the period of transplantation from further analyses because it

TABLE 3. ITT Transplant Benefit Estimations in Months in Different Subgroups

Variables	Benefit in Months (n of Patients): No	Benefit in Months (n of Patients): Yes	*d* Value Between Groups (95% CI)	Difference
WT ≥120 days	25.5 (1,140)	24.0 (963)	0.06 (0.01-0.13)	Very small
Age at listing ≥60 years	25.5 (1,372)	23.6 (731)	0.07 (0.02-0.16)	Very small
Last AFP ≥20 ng/mL	27.0 (1,439)	20.3 (664)	0.26 (0.17-0.36)	Small
MC-IN at LT or DO	34.5 (496)	22.8 (1,607)	0.47 (0.37-0.57)	Moderate*
WL inscription before 2001	27.3 (1,802)	10.4 (301)	0.69 (0.57-0.81)	Large†
Last AFP ≥1,000 ng/mL	25.4 (2,040)	6.8 (63)	0.74 (0.49-0.99)	Large*
mRECIST progression disease	29.2 (1,612)	10.6 (491)	0.78 (0.67-0.88)	Large*
MELD at LT or DO ≤13	39.1 (708)	19.8 (1,395)	0.81 (0.73-0.90)	Large*
mRECIST complete response	28.7 (1,723)	7.2 (380)	0.90 (0.79-1.01)	Large*

Benefit Groups*

Group	Benefit in Months	n of Patients (%)	
No benefit	0	405 (19.2)	3-4 negative factors
Small benefit	20	897 (42.7)	2 negative factors
Moderate benefit	40	693 (33.0)	1 negative factor
Large benefit	60	108 (5.1)	No negative factors

Continuous variables in Table 3 were dichotomized using relevant cut-off values used in the literature.[5,6,11,12]
Results are reported as means; *d* value (effect size) values <0.1 indicate very small differences; between 0.1 and 0.3 and between 0.3 and 0.5 indicate small and moderate differences, respectively, and >0.5 indicate large differences.
*Four risk factors were considered for constructing the benefit groups: MELD ≤13; MC-IN; mRECIST progression disease or complete response; AFP ≥1,000 ng/mL. Benefit values in the groups were rounded to the nearest whole number.
†WL inscription before or after 2001 was not considered in the final group stratification because the period of WL inscription showed a very poor effect on survival benefit estimates (Supporting Tables S3-S4) and it was not considered useful for the evaluation of the benefit in patients enlisted now.
Abbreviations: CI, confidence interval.

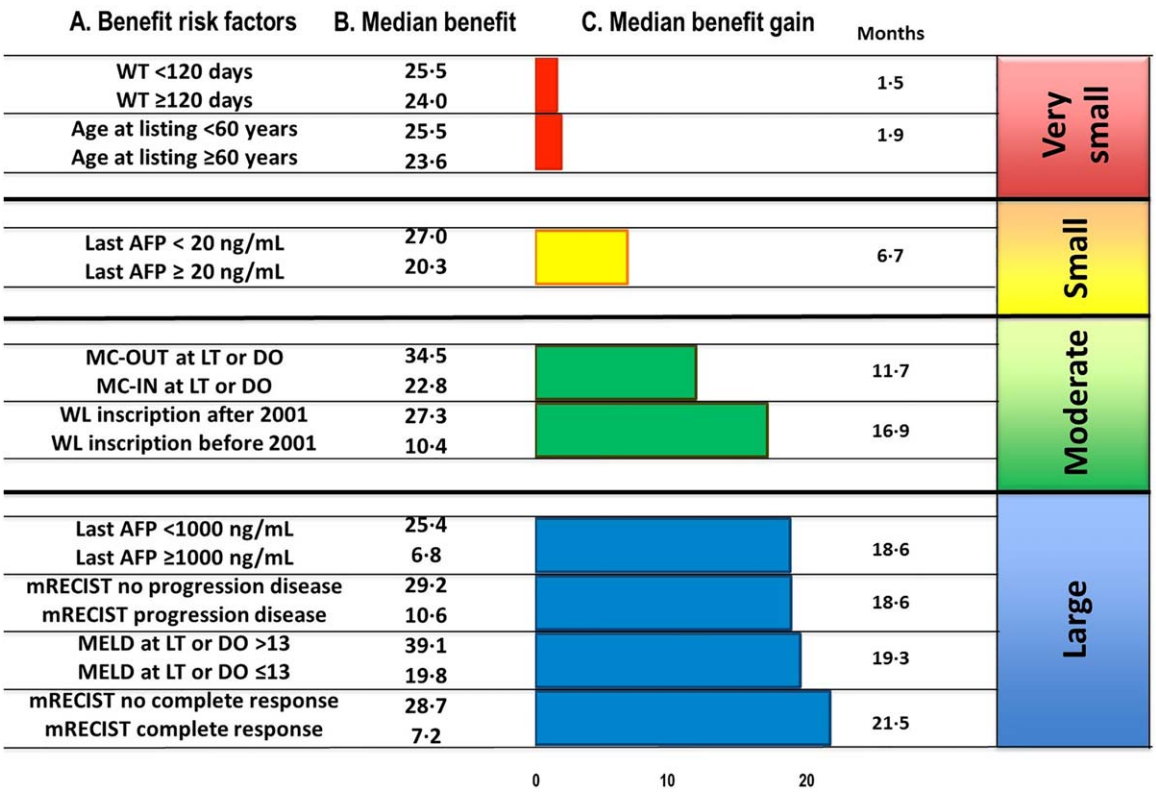


FIG. 1. Benefit risk factors and benefit gains. For each of the nine reported risk factors (section A), two median benefits are reported according to specific threshold values (section B). Median benefit gains are calculated for each factor by difference between the reported median benefits (section C). Benefit gains are arbitrary grouped in four levels (very small, small, moderate, and large benefit).

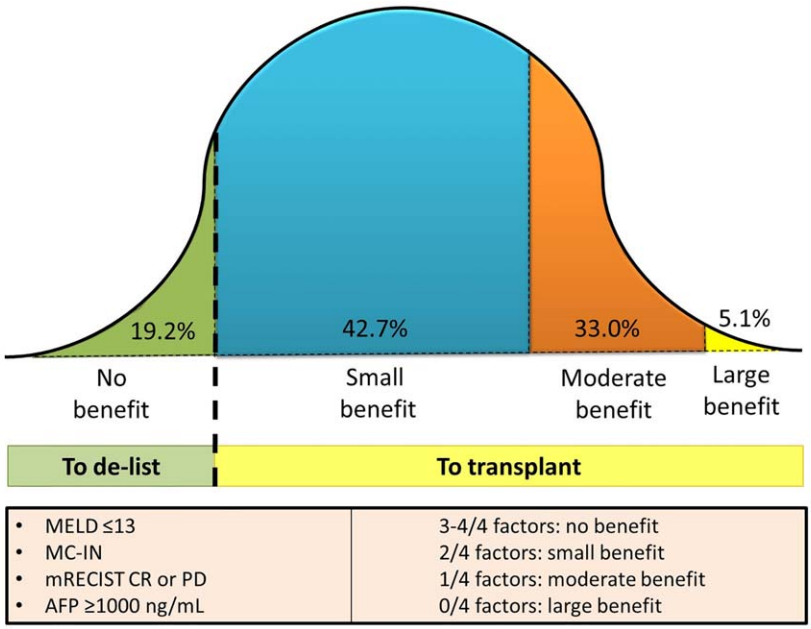
was considered as useless when applying to patients transplanted presently. When doing so, four benefit groups could be identified according to the presence of the remaining four risk factors. Patients presenting a combination of three to four factors (no-benefit group: n = 405 of 2,103; 19.2%) had no benefit in being transplanted compared to alternative therapies (median value of improved survival: 0 months). Patients in the small (two risk factors: n = 897; 42.7%) and moderate (one risk factor: n = 693; 33.0%) groups displayed improved survival benefits of 20 and 40 months, respectively. Conversely, patients without any risk factor (large-benefit group: n = 108; 5.1%) had the highest benefit reaching 60 months (Table 3; Fig. 2). Different contour plots deriving from the combination of the different risk factors are displayed in Supporting Fig. S1.

Discussion

Twenty years after their introduction, MC are no longer considered to be the best criterion to select HCC patients for LT.[25] However, the best compromise between the need to justifiably raise the number of transplantable patients and the necessity to minimize the risk for recurrence, without contemporaneously harming non-HCC patients on the WL, is still to be established.[19]

Aiming at squaring the circle, a recent article by Mazzaferro interestingly reported that the only way to frame the complex scenario of LT for HCC is the ability to capture in a weighty manner tumor evolution in relation to its treatment, aiming to modulate scores able to estimate the risk of pre-LT DO and post-LT benefit.[26] So, morphology "per se" is insufficient to optimize selection and allocation, and new criteria, possibly focused on "progression" rather than on static tumor characteristics, should be used in order to better identify those patients in real need for LT.[4]

In Italy, a demanding effort has been made with the intent to build an algorithm based on the principles of urgency, utility, and transplant benefit, clearly underlying the inequity of a purely MELD-based HCC allocation model. Different variables (response to LRT, WT, and AFP) all have been advocated as possible



Scenario	AFP (ng/mL)	MELD	mRECIST	MC status	Factors	Benefit months	Clinical decision
#1	20	6	CR	IN*	3	0	De-list
#2	1200	15	PD	IN	3	0	De-list
#3	20	6	PR	IN	2	20	LT with low priority
#4	1200	15	PD	OUT	2	20	LT with low priority
#5	1200	15	SD	OUT	1	40	LT with mild priority
#6	20	15	No LRT	IN	1	40	LT with mild priority
#7	20	15	No LRT	OUT	0	60	LT with high priority
#8	20	15	PR	OUT	0	60	LT with high priority

*** In case of CR, MC status has been arbitrarily considered as MC-IN.**

FIG. 2. Incidence of the four different "benefit groups" in the examined population.

selection criteria to be used in such a "benefit scenario."[27] However, the main limit of their use in the setting of benefit is that no scientific evidence exists on their effective contribution in terms of survival.

In the present study, four different risk factors connected with poor ITT benefit have been identified: radiological progression/complete response, AFP increase, MC-IN status, and low MELD score.

Several previously published studies corroborate our findings. The recent article by Mehta et al. reported on a selected population of HCC T2 patients waiting for LT with a very low 2-year probability of DO (only 1.6%). Tumor morphology (1 tumor of 2-3 cm), radiological response to LRT (complete response after the first treatment), and biological behavior (AFP level stably normal after the first LRT) selected these patients.[28]

Several European studies similarly confirmed the paramount role of radiological response,[8,9,11] and AFP modification post-LRT,[6,7,11,18] as the better selection criterion of HCC patients awaiting LT. The multicentric EurHeCaLT study showed that the combination of radiological response and AFP slope allowed to better discriminate "low-risk" from "high-risk-for-recurrence" patients, and this independently from their MC-IN or OUT status.[12] Two recent scores, all focusing on the HCC selection process, further underlined the importance of combining biology and morphology in order to further improve results. Interestingly, the TRAIN score, based on the combination of AFP slope, radiological progression, inflammatory markers, and WT, was superior with respect to MC in predicting patient death during the WT in a long-WT population, whereas it was superior in predicting post-LT recurrence in case of short WT.[11] The MORAL score, incorporating

inflammatory markers, AFP, and tumor morphology, also showed to be significantly superior to MC, with an area under the curve of 0.82 versus 0.63 for predicting post-LT HCC recurrence.[29]

Also, the fact that MC-IN status was connected with poor survival benefit had been observed in a multicenter Italian study including 1,328 patients: Survival benefit was obtainable in patients having advanced HCC, and this was regardless of the "nodule number-size criteria" (as MC are).[30] In other terms, the benefit increases when the number of nodules and the dimensions of the tumor contemporaneously increase, on the condition that radiological findings and AFP do not progress.

Various articles already focused on the role of MELD increase as a cause of increased benefit. A U.S. study clearly observed that the increase in MELD points corresponds to a progressive survival benefit increase in HCC and non-HCC patients, ranging from just a few months in patients with MELD score of 6-8 to 4 years in patients with MELD score of 36-40.[19] Another Italian study similarly reported that MELD score increase was associated with a better benefit both in HCC and non-HCC patients; interestingly enough, this study observed that an equation based on the combination of MELD and AFP (the "HCC-MELD" equation) allowed the calculation of a numerical score for HCC patients, with the intent to calibrate their transplant benefit with the one observed in non-HCC patients having the same MELD value.[18] This finding was also observed in the present series, in which MELD and AFP were factors allowing to discriminate low- and high-benefit patients.

Despite the fact that each risk factor has already been singularly investigated in other studies focusing on the prediction of survival in HCC patients, one should note that the present study presents several innovations. First, a concept of ITT survival benefit has been proposed, as well as a statistical methodology that has been created for calculating it. The rationale for the proposal of this concept is to further increase the balancing between pure priority and pure utility: The integration of two large populations of LT and non-LT patients in the creation of the ITT benefit statistical model allowed, in fact, to better calibrate the role of the evaluated variables in both settings.

Second, radiological response to LRT has been investigated in a benefit-related analysis. The lack of studies investigating its role in the LT selection process may be explained by the fact that several large cohorts include a smaller number of LRT cases compared to our series; moreover, radiological response has not been systematically collected in large populations, so only small mono-center studies (apart from the reported EurHeCaLT study) have been investigated.[12]

Third, all of the investigated variables have been connected in order to create different ITT benefit groups, and to define categories of patients that would benefit from LT.

In fact, when three to four of the analyzed risk factors are present in a single patient, ITT benefit was nil. Such a result is extremely important, because patients presenting three to four risk factors represented 19% of the investigated population. Interestingly enough, this specific no-benefit group consisted of two main patient categories. On one side, MC-IN patients with low MELD showing radiological-biological progression were observed. These patients are similar to those patients already reported on in the study by Mehta et al., in which poor radiological response and increased AFP corresponded to higher percentages of DO.[28]

On the other hand, MC-IN patients with low MELD with complete radiological response corresponded to the Transplantable Tumor (TT)0 category reported by Mazzaferro, in which the cancer is "zeroed" by LRT/resection during the WT.[26] In both scenarios, such patients should be delisted: in the first case because of the poor benefit connected with an advanced cancer and in the second case because of a poor benefit associated with a completely healed tumor.

Conversely, when looking at the "high" ITT benefit group, an extraordinary benefit (5 years) in comparison to not-transplanted patients presenting the same characteristics was observed. As a consequence, it looks obvious that such a patient population should be surely considered for LT. Despite the fact that this group consists of high-MELD MC-OUT patients (without any evidence of radiological-biological progression), thus potentially being associated with more perioperative mortality and post-LT recurrence, the benefit in transplanting (and even prioritizing) them is clear. Moreover, it should be underlined that such a population is really small, representing no more than 5% of the entire investigated population. Therefore, prioritization of such a population should only marginally impact on the number of used grafts, mainly if we consider on the opposite the great number of potentially "preservable" livers if we delist the patients with no ITT benefit (as a reminder, this group represents 19% of all the investigated cases!).

When considering the group of patients presenting "low" ITT benefit (patients with two risk factors: 20 months of benefit), one should keep in mind that the

decision to transplant these patients has to be seen in the context of the opportunity to perform an LT without harming the group of listed non-HCC patients ("concept of equity").[31] Such a concept has been very elegantly demonstrated by Volk in the U.S. population, in which the decision to transplant an HCC patient was justified only if a minimal survival threshold was reached: Only in this case, in fact, the benefit of transplanting tumor patients outweighed the harm for not transplanting non-HCC patients.[32] Similar results were also reported in a mono-center experience from Italy.[33] As a consequence, patients presenting only small benefit (corresponding to 42.7% of our entire investigated population) should be carefully considered, mainly when evaluated in a low-volume center. As an example, an MC-OUT patient with low MELD and AFP $\geq$1,000 ng/mL should be closely evaluated in a low-volume center in light of his high recurrence risk.

The present study did not explore the opportunity to propose a more equal organ allocation model among enlisted HCC and non-HCC patients in terms of priority score for LT, such as the "HCC-MELD" model did.[18] Moreover, this latter score is based only on AFP and MELD and it was calculated only in T2 HCC patients, whereas the present score presents a higher complexity (AFP, MELD, radiological response, and initial MC status). The development of an equation able to recalibrate the whole allocation process (i.e., including both selection of patients for listing and prioritization of listed patients) among non-HCC and HCC patients should be further explored.

The authors concede that the present study has some limitations. First of all, it is a retrospective, collaborative, nonrandomized study covering a 30-year period. Consequently, some statistical and methodological limits exist. However, we feel confident that the largeness of the investigated population and the rigorous adherence to the statistical analysis guidelines may have counteracted these negative parameters. Moreover, the introduction of the period of WL inscription as a covariate in the multivariate models further minimizes the possible errors deriving from a "period-dependent" selection.

Another possible limit derives from the fact that allocation disparities may be caused by parameters not investigated other than tumor characteristics (i.e., blood group): unfortunately, the retrospective character of the present study did not give the opportunity to fully investigate such aspects.

The ITT survival benefit of LT enables better discrimination among HCC patients waiting for LT in relation to their real need for transplantation. Such a stratification may lead to an improved and more equitable liver allocation. New aspects such as radiological response post-LRT should be implemented in clinical practice as a selection parameter to be used in HCC patients. The combination of radiological and biological tumor characteristics should be considered to be the gold standard for HCC selection instead of the conventionally used "only morphological" criteria.

APPENDIX

EurHeCaLT Study Group Collaborators

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