Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis

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Summary

Background Patients undergoing liver transplantation for hepatocellular carcinoma within the Milan criteria (single tumour ≤5 cm in size or ≤3 tumours each ≤3 cm in size, and no macrovascular invasion) have an excellent outcome. However, survival for patients with cancers that exceed these criteria remains unpredictable and access to transplantation is a balance of maximising patients' chances of cure and organ availability. The aim of this study was to explore the survival of patients with tumours that exceed the Milan criteria, to assess whether the criteria could be less restrictive, enabling more patients to qualify as transplant candidates, and to derive a prognostic model based on objective tumour characteristics, to see whether the Milan criteria could be expanded.

Methods Data on patients who underwent transplantation for hepatocellular carcinoma despite exceeding Milan criteria at different centres were recorded via a web-based survey completed by specialists from each centre. The survival of these patients was correlated retrospectively with the size of the largest tumour nodule, number of nodules, and presence or absence of microvascular invasion detected at pathology. Contoured multivariable regression Cox models produced survival estimates by means of different combinations of the covariates. The primary aim of this study was to derive a prognostic model of overall survival based on tumour characteristics, according to the main parameters used in the Tumour Node Metastasis classification. The secondary aim was the identification of a subgroup of patients with hepatocellular carcinoma exceeding the Milan criteria, who achieved a 5-year overall survival of at least 70%—ie, similar to the outcome expected for patients who meet the Milan criteria.

Findings Over a 10-month period, between June 25, 2006, and April 3, 2007, data for 1556 patients who underwent transplantation for hepatocellular carcinoma were entered on the database by 36 centres. 1112 patients had hepatocellular carcinoma exceeding Milan criteria and 444 patients had hepatocellular carcinoma shown not to exceed Milan criteria at post-transplant pathology review. In the group of patients with hepatocellular carcinomas exceeding the criteria, the median size of the largest nodule was 40 mm (range 4–200) and the median number of nodules was four (1–20). 454 of 1112 patients (41%) had microvascular invasion and, for those transplanted outside the Milan criteria, 5-year overall survival was 53·6% (95% CI 50·1–57·0), compared with 73·3% (68·2–77·7) for those that met the criteria. Hazard ratios (HR) associated with increasing values of size and number were 1·34 (1·25–1·44) and 1·51 (1·21–1·88), respectively. The effect was linear for size, whereas for number of tumours, the effect tended to plateau above three tumours. The effect of tumour size and number on survival was mediated by recurrence (b=0·08, SE=0·12, p=0·476). The presence of microvascular invasion doubled HRs in all scenarios. The 283 patients without microvascular invasion, but who fell within the Up-to-seven criteria (hepatocellular carcinomas with seven as the sum of the size of the largest tumour [in cm] and the number of tumours) achieved a 5-year overall survival of 71·2% (64·3–77·0).

Interpretation More patients with hepatocellular carcinoma could be candidates for transplantation if the current dual (yes/no) approach to candidacy, based on the strict Milan criteria, were replaced with a more precise estimation of survival contouring individual tumour characteristics and use of the up-to-seven criteria.

Funding Specific funding was not used to do this study.

Introduction

Early-stage hepatocellular carcinoma is recognised as an excellent indication for liver transplantation. The size of the tumour, the number of tumours, and the presence of vascular invasion have been incorporated into the so-called Milan criteria, which predicts a low incidence of recurrence (about 10%) for transplant patients with a single tumour of 5 cm or less in size or with many tumours (up to a maximum of three, each 3 cm or less in size), and no macroscopic vascular invasion. Since the first prospective series done more than 10 years ago,[1,2] these criteria have been validated in several centres around the world, adopted as a prioritisation tool in the United Network of Organ Sharing (UNOS), and

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incorporated in the Tumour Node Metastasis (TNM) and Barcelona Clinic Liver Cancer (BCLC) staging systems for hepatocellular carcinoma.[3–6]

In recent years, several studies have reported a good outcome for some patients transplanted outside these conventional criteria and the dichotomous yes/no nature of these criteria has been challenged for being too strict, because they exclude specific subgroups with meaningful, albeit lower, chances to benefit from transplantation. Furthermore, some patients might be excluded from transplantation as a result of the improvement in the accuracy of imaging techniques that enable the identification of very small lesions (<1 cm), which were undetectable a decade ago. Most of the studies on patients exceeding Milan criteria, however, are retrospective, with only a small number of patients, disease of variable severity, and short follow-up.[7–12] Overall, no precise information can be extracted from these studies, other than the further the distance from conventional limits, the higher the price in terms of malignant recurrences.[7]

The aim of the current study was to explore the area outside the conventional criteria for liver transplantation in hepatocellular carcinoma, by use of morphological (size of the largest tumour and number of tumours) and histological (microscopic vascular invasion) parameters in a large cohort of patients with adequate follow-up. The working postulation was that beyond the conventional eligibility criteria for transplantation for patients with hepatocellular carcinoma, a continuum in outcome probabilities could be identified linked to characteristics assessed in the TNM classification.[5]

Methods

Study background and data collection

The study design was presented during the International Liver Transplantation Society meeting held in Milan, Italy, in 2006 and a web-based survey of patients who received liver transplantation for hepatocellular carcinoma exceeding the Milan criteria was proposed. The website on which the survey can be completed (www.hcc-olt-metroticket.org) was built at the Clinical Trial Office of the National Cancer Institute of Milan, supported only by grants for investigator-initiated studies. The website was prepared according to the privacy and security regulations for sensitive data of both the European Union and the USA.

The **Metroticket Calculator** is available at http://www.hcc-olt-metroticket.org/calculator

After registration on the website, investigators from each centre were asked to enter data, with no restrictions for time of transplantation and tumour stage, of patients who underwent liver transplantation for hepatocellular carcinoma exceeding Milan criteria. The required dataset for each patient (table 1) was kept to a single-page form, to encourage maximum participation by as many centres as possible. Data on size of the main tumour, number of tumours, vascular invasion, grading, living donor versus cadaveric donor, year of transplantation, recurrence, and survival were based on the final pathology review of the explanted liver, and central review of pathology reports was not planned.

Patients who fell within conventional criteria could be entered on the database at the discretion of the investigators, because the database could also be used as a permanent registry for all patients who undergo transplant for hepatocellular carcinoma at each centre.

A professional website administrator and a data manager regularly checked the system and guaranteed security and privacy. Inconsistencies were corrected by contact with investigators in each centre. Data were analysed with approval by the local Institutional Review Board granted on the condition that all data was anonymised.

Data presentation and study endpoints

The primary aim of this study was to derive a prognostic model of overall survival based on tumour characteristics, according to the main parameters used in the TNM classification system: size of the largest tumour, number of tumours (morphology-related), and microvascular invasion (biology-related). Survival was chosen because it was considered to be the most reliable and unbiased endpoint in the research of hepatocellular carcinoma[13] and because of the assumption that in such a large patient population, causes of death other than tumour recurrence would not have been affected by the variables chosen for the study.

According to a previous proposal, data were plotted in a Cartesian plot, with size of the largest tumour on the X-axis and number of tumours on the Y-axis.[7]

Vascular invasion was included in the model as a biological variable rather than tumour grading because it was more consistently reported in the medical records and because of its lower interobserver variation compared with tumour grading.

The model was set up to give a mathematical function, which resulted in the prediction of survival after transplantation on the basis of the three covariates: size, number, and microvascular invasion. A by-product tool was the "Metroticket Calculator", a piece of software that is accessible online and which can calculate 3-year and 5-year overall survival probabilities, with confidence intervals, of a given patient on the basis of the characteristics of the hepatocellular carcinoma.

The secondary aim of this study was the identification of a subgroup of patients with hepatocellular carcinoma exceeding Milan criteria, who achieved a 5-year overall survival of at least 70%, which is similar to the outcome expected for patients who meet conventional criteria.[9–12]

Statistical analyses

Overall survival was defined as the time interval between liver transplantation and death from any cause. Time was censored at the date of last follow-up assessment for patients who were still alive. Survival curves were estimated using the Kaplan-Meier method.

In the main analyses, size of the largest tumour, number of tumours, and presence or absence of microvascular invasion were entered into multiple Cox regression models, in this order, as covariates.[14] Tumour size and number were modelled as continuous variables by using three-knot restricted cubic splines,[15] together with size×number linear and non-linear interaction terms. Because data were sparse when tumour size was more than 150 mm or number of tumours was greater than 15, higher values were truncated at these thresholds. Microvascular invasion was modelled as a dummy variable (1/0, depending on whether it was present at post-transplant histological assessment). By backward selection, models were simplified on the basis of the Akaike Information Criterion.[16] The Cox proportional hazards assumption was checked by use of the smoothed plots of Schoenfeld residuals.[17] Cox model results were shown either by means of hazard ratio (HR) estimates, together with corresponding 95% CIs and Wald's test p values, or by graphical plots. The latter included log-relative hazard plots, showing the shape of the relation between the relative hazard of death and size or number of tumours, and contour plots showing the joint effect of the model covariates on survival probability.

The quality of the above Cox model was checked in several ways. First, for internal model validation, bootstrap resampling was applied to detect model overfitting.[18,19] Second, for checking the consistency of outcomes in the individual centres, we estimated the standardised mortality ratio (SMR), namely the ratio between the number of deaths noted and the number predicted by the Cox model in each centre. The SMRs were then fitted using the generalised linear mixed model with a Poisson response variable, and centre as a random factor.[19,20]

Finally, to assess whether the covariate effect on overall survival was mainly associated with the occurrence of tumour recurrence, we fitted Cox models that included recurrence as a time-dependent covariate, together with the prognostic score derived from the main Cox model analyses.

Although no formal sample-size calculation was made beforehand, the high number of deaths (more than 500) compared with the number of Cox model variables (five at most) implied that the "ten events per variable" rule was largely exceeded, thus implying sufficient accuracy and precision of regression estimates.[21]

Statistical tests were considered significant when the corresponding p value was less than 5%. SAS[22] and R[23] software were used to do the modelling and statistical calculations.

Role of the funding source

This was an investigator-led study and no specific financial support was obtained. Investigators from the National Cancer Institute of Milan were partially funded by the Italian Association for Cancer Research (AIRC)

	Number of patients (N=1556)	Milan criteria		p value
		Within (n=444)	Outside (n=1112)	
Transplant year, n (%)				<0·0001
1984–90	53 (3·4)	0 (0)	53 (4·8)	
1991–95	213 (13·7)	54 (12·2)	159 (14·3)	
1996–2000	391 (25·1)	93 (20·9)	298 (26·8)	
2001–06	899 (57·8)	297 (66·9)	602 (54·1)	
Transplant type, n (%)				0·006
Cadaveric donor	1404/1525 (92·1)	421/443 (95·0)	983/1082 (90·9)	
Living donor	121/1525 (7·9)	22/443 (5·0)	99/1082 (9·1)	
Not available	31 (··)	1 (··)	30 (··)	
Age, years				0·216
Median (IQR)	55 (50–60)	55 (50–59)	56 (50–61)	
Range	10–75	30–69	10–75	
Range of tumours, n (%)				<0·0001
1	404 (26·0)	257 (57·9)	147 (13·2)	
2–3	569 (36·6)	187 (42·1)	382 (34·4)	
4–5	338 (21·7)	0 (0)	338 (30·4)	
6–10	203 (13·0)	0 (0)	203 (18·3)	
>10	42 (2·7)	0 (0)	42 (3·8)	
Number of tumours				<0·0001
Median (IQR)	3 (1–5)	1 (1–2)	4 (2–5)	
Range	1–20	1–3	1–20	
Maximum tumour size, mm				<0·0001
Median (IQR)	35 (22–50)	20 (15–30)	40 (30–60)	
Range	1–200	1–50	4–200	
Grading, n (%)				0·003
G1	284/1113 (25·5)	50/197 (25·4)	234/916 (25·5)	
G2	550/1113 (49·4)	115/197 (58·4)	435/916 (47·5)	
G3	279/1113 (25·1)	32/197 (16·2)	247/916 (27·0)	
Not available	443 (··)	247 (··)	196 (··)	
Vascular invasion, n (%)				<0·0001
No	977/1475 (66·2)	361/405 (89·1)	616/1070 (57·6)	
Yes	498/1475 (33·8)	44/405 (10·9)	454/1070 (42·4)	
Not available	81 (··)	39 (··)	42 (··)	
Follow-up, months				..
Median (IQR)	53 (25–95)	47 (25–85)	57 (25–97)	
Patient status, n				..
Alive (with/without recurrence)	60/904	8/327	52/577	
Dead (with/without recurrence)	251/341	11/98	240/243	
Recurrence-free survival (95% CI), %				<0·0001
5 years	72·6 (69·6–75·3)	94·5 (91·4–96·5)	64·1 (60·3–67·6)	
10 years	68·2 (64·5–71·5)	94·5 (91·4–96·5)	58·1 (53·5–62·4)	
Overall survival (95% CI), %				<0·0001
5 years	59·1 (56·1–61·9)	73·3 (68·2–77·7)	53·6 (50·1–57·0)	
10 years	46·8 (43·0–50·5)	69·6 (63·7–74·8)	38·7 (34·2–43·1)	
Median overall survival (IQR), months	95 (22–nr)	nr (46–nr)	75 (18–nr)	

IQR=interquartile range. nr=not reached.

Table 1: **Main characteristics of patients with hepatocellular carcinoma undergoing liver transplantation**

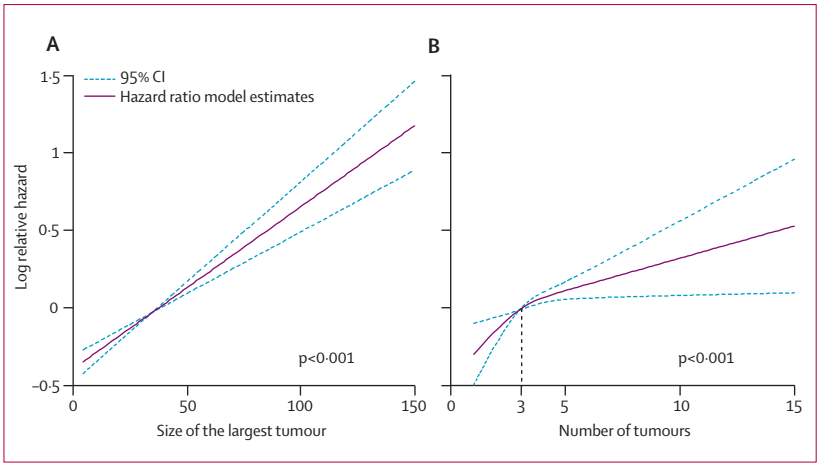

Figure 1: **Log-relative risk of death related to size of the largest tumour (A) and number of tumours (B)**
(A) Number of tumours was fixed at three (median value of the number distribution). (B) Size was fixed at 35 mm. The increase in risk in patients with hepatocellular carcinoma is clearly related to the progressive increment of either the size or number with different patterns (see text).

	HR (95% CI)	p value
Size of largest tumour (50 *vs* 22 mm)		<0·001
N=1 (1st quartile)	1·38 (1·27–1·51)	
N=3 (median)	1·34 (1·25–1·44)	
N=5 (3rd quartile)	1·30 (1·20–1·40)	
Number of tumours (5 *vs* 1)		<0·001
S=22 mm (1st quartile)	1·55 (1·23–1·97)	
S=35 mm (median)	1·51 (1·21–1·88)	
S=50 mm (3rd quartile)	1·46 (1·18–1·81)	

Data derived from figure 1. HR=hazard ratio. N=number. S=size.

Table 2: **Risk of death related to size of the largest tumour and number of tumours**

and the Oncology Research Funds of the Italian Ministry of Health. All authors were responsible for data collection and interpretation. V Mazzaferro, R Miceli, M Schiavo, L Mariani, and P Majno had full access to all data, and V Mazzaferro and P Majno had the final responsibility to submit for publication.

Results

During the 10-month recruitment period, between June 25, 2006, and April 3, 2007, 36 liver-transplantation centres entered data on the website, with an overall data collection of 1556 patients who underwent liver transplantation for hepatocellular carcinoma: 1274 patients (81·9%) from 31 centres in Europe, 269 patients (17·3%) from four centres in America, and 13 patients (0·8%) from one centre in Asia. The study population included 1112 patients (71·5%) with hepatocellular carcinoma exceeding Milan criteria, and 444 patients (28·5%) not exceeding such criteria at post-transplant pathology review.

Characteristics of the collected series and cumulative data on overall survival are summarised in table 1.

More than 50% of patients with hepatocellular carcinoma exceeding conventional criteria (602 of 1112 patients) underwent transplant between 2001 and 2006. In the group of patients exceeding the criteria (n=1112), the median number of tumours was four (interquartile range [IQR] 2–5) and the median size of the tumours was 40 mm (30–60). 583 of 1112 patients (52·4%) had multifocal disease exceeding three nodules. These characteristics were significantly different to those of the group of patients with hepatocellular carcinoma adherent to Milan criteria (p<0·0001). With respect to histological surrogates of biological behaviour, hepatocellular carcinoma exceeding conventional criteria showed a significantly higher percentage of undifferentiated grade 3 tumours (p=0·003) and vascular invasion (p<0·0001) than hepatocellular carcinomas that fell within the Milan criteria. However, due to the high number of patients with missing data for tumour grading (443 of 1556 [28·5%]) a meaningful consideration of tumour grading in the survival model was precluded, whereas information on vascular invasion was available for most patients (1475 of 1556 [94·8%]) included in the database. In patients with hepatocellular carcinoma exceeding the Milan criteria, vascular invasion was present in 454 of the 1070 patients (42·4%) with data available versus 44 of 405 patients (10·9%) with hepatocellular carcinoma within the Milan criteria.

Overall median follow-up was 53 months (IQR 25–95), with a total number of 592 deaths from any cause (483 patients [81·6%] with hepatocellular carcinomas exceeding Milan criteria), and tumour recurrence was noted in 311 patients overall. This resulted in a significant difference in the observed 5-year overall survival: 53·6% (95% CI 50·1–57·0) for patients with hepatocellular carcinomas exceeding the Milan criteria versus 73·3% (68·2–77·7) for those with hepatocellular carcinomas within the Milan criteria (p<0·0001).

Results of Cox regression models, either based solely on the size of the largest tumour and number of tumours, or including microvascular invasion, are shown in figure 1 and table 2, and figure 2. These models, after applying a backward selection procedure, included a linear term for size, a cubic spline for number, and the linear-by-linear interaction size-by-number.

Because of the presence of interaction, the effect of size (or number) could not be represented separately, and thus is shown for different values of each of the two variables. Estimated HRs for the increase in the relative hazard of death associated with size or number progression were about 1·3 and 1·5, respectively (table 2). For example, patients with five tumours were estimated to have a risk 1·55-times higher than patients with one tumour of 22 mm in size (1st quartile of the size distribution; figure 1), or slightly lower at 1·46-times for a tumour of 50 mm in size (3rd quartile; figure 1 and table 2). Conversely, patients with a tumour of 50 mm in size were estimated to have about 1·38-times the risk of patients with a hepatocellular carcinoma of 22 mm in size, and this risk for a 50-mm

versus 22-mm tumour did not change with an increasing number of tumours (table 2).

Although the effect of size was linear, the covariate number of tumours showed a non-linear behaviour in which the increment was sharp for up to three tumours and weak thereafter (figure 1). Incidentally, such a result supported the number of three tumours as the accepted cut-off for the criteria currently used for transplant candidacy.

A doubling in the hazard of death was associated with the presence of microvascular invasion. The median number of tumours in the subgroup of patients with hepatocellular carcinomas not showing microvascular invasion was two (IQR 1–4), whereas in the subgroup of patients with tumours presenting microvascular invasion the median number was three (2–5). The corresponding estimates for median tumour size were 30 mm for no microvascular invasion (20–45) and 45 mm for the presence of microvascular invasion (30–65 mm). Both differences were significant (p<0·0001).

Figure 2 shows 5-year overall survival estimates as a function of different values of size, number, and microvascular invasion. Contour lines connect points of equal probability, and are shown to aid with the clinical interpretation of the model. As a practical tool for individualised calculation of survival probability, a freely accessible software tool was developed, called the Metroticket Calculator (link to website noted earlier), which provides 3-year and 5-year survival estimates and 95% CIs for an individual patient on the basis of their tumour characteristics.

A search for combinations of tumour characteristics exceeding the Milan criteria, but resulting in an estimated 5-year overall survival of at least 70% generated a subgroup that, in the absence of microvascular invasion, fulfilled the so-called up-to-seven criteria, with seven being the result of the sum of size (in cm) and number of tumours for any given hepatocellular carcinoma. This includes all combinations of a given hepatocellular carcinoma from one nodule up to 6 cm in size (1+6=7) to many tumours fulfilling seven as the sum of the size plus number (ie, two tumours up to 5 cm in size, three tumours up to 4 cm in size, four tumours up to 3 cm in size, and five tumours up to 2 cm in size). The 5-year overall survival estimate for this subgroup of 283 patients was 71·2%, (95% CI 64·3–77·0), which was not significantly different from the 5-year overall survival for the 444 patients who had hepatocellular carcinomas within the Milan criteria, irrespective of microvascular invasion (figure 3; 73·3% (68·2–77·7). Patients exceeding the up-to-seven criteria, plus patients with microvascular invasion who were beyond the Milan criteria and within the up-to-seven criteria (829 patients), had a 48·1% (44·1–52·0) 5-year overall survival (p<0·001).

The occurrence of microvascular invasion at any size-and-number category was paralleled by a significant deterioration in patient outcome, both for overall survival and cumulative incidence of post-transplant recurrence (table 3). This was assessed in a uniform way, according to international guidelines.[4] Differences in survival in the identified prognostic categories were deemed significant regardless of graft origin (ie, deceased *vs* living donor).

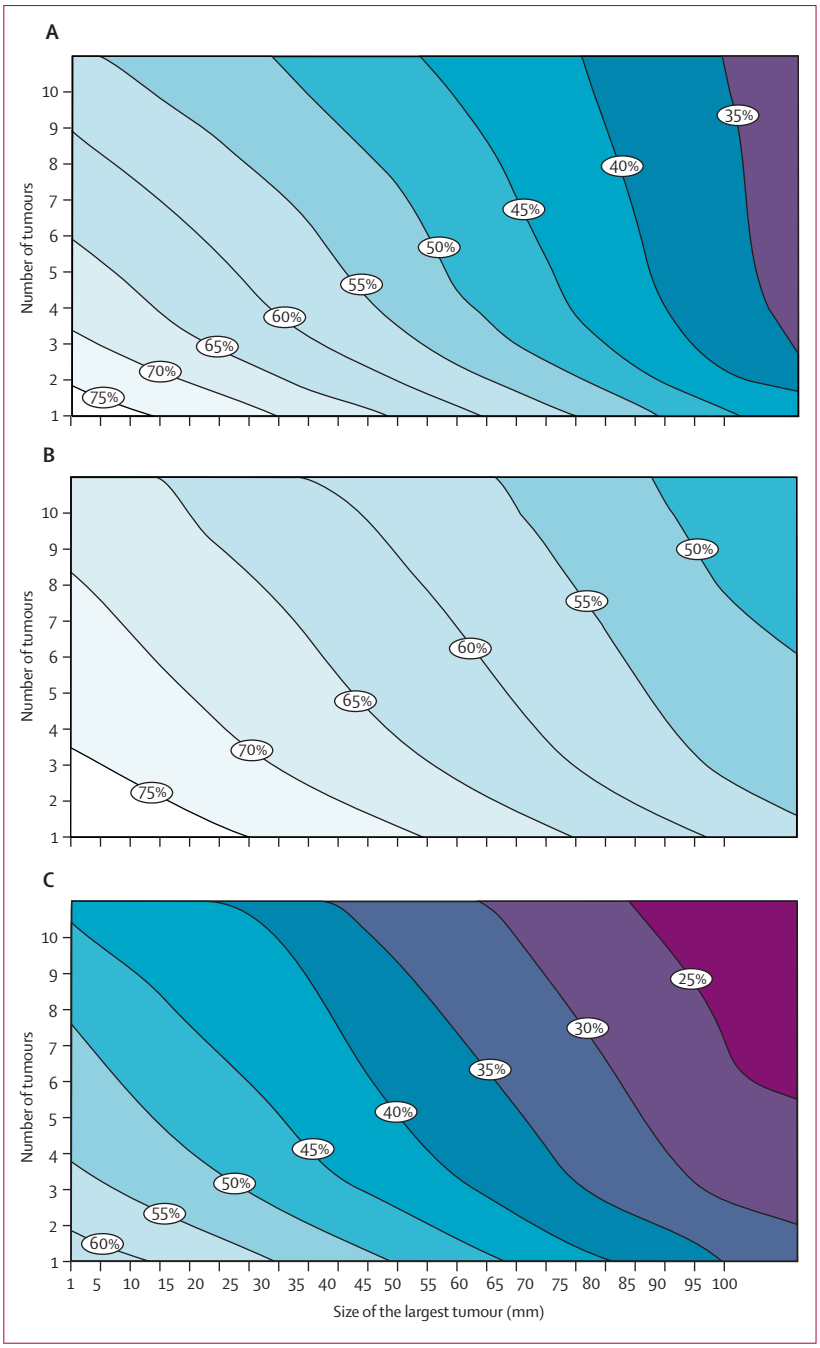

Figure 2: **Contour plot of the 5-year overall-survival probability according to size of the largest tumour, number of tumours, and presence or absence of microvascular invasion**
(A) Survival estimates according to size and number, not considering microvascular invasion (median SE 4·2% [interquartile range 3·6–5·2]). (B,C) Survival estimates according to absence (B) or presence (C) of microvascular invasion. Presence of microvascular invasion approximately halves the survival predicted in the absence of the same variable: absent (6·3% [5·7–7·1]); present (3·7% [3·1–4·7]).

A significant increase in the proportion of hepatocellular carcinomas with microvascular invasion was noted as the limit of the Milan criteria was moved to the up-to-seven criteria and beyond (31 of 187 [16·6% *vs* 95 of 324 [29·3%] *vs* 287 of 572 [50·2%], respectively; figure 4).

Although microvascular invasion was the strongest covariate affecting patient survival, high tumour grade (grade 3) significantly affected outcome (table 1) and significantly increased in prevalence from 16·0% (30 of 187) to 21·3% (69 of 324) to 30·6% (175 of 572), as tumour staging progressed from Milan criteria, to the up-to-seven category, and beyond (p<0·0001; figure 4). However, data on grading of hepatocellular carcinoma were not available in 443 of 1556 (28·5%) of the patients, preventing grade 3 from being included in the predictive survival model.

The prediction of tumour recurrence by the model paralleled patient survival, but was less precise because of a decreased accuracy of the data in terms of interval to recurrence and treatment efficacy on survival. As expected, due to the high number of events compared with the number of model parameters, and the use of a selection procedure that was not based on multiple testing, bootstrap validation showed that overfitting was negligible, and therefore no adjustment of Cox model estimates was needed. The effect of size-and-number covariates on overall survival, as summarised by the prognostic score in the main analysis, was almost totally abolished when tumour recurrence was included as a time-dependent covariate (regression coefficient b=0·08, SE=0·12, p=0·476). This shows that the prognostic effect of size-and-number on survival is mediated by the occurrence of tumour relapse. Results were less clear-cut when adding in the variable microvascular invasion, in that the regression coefficient associated with the prognostic score derived from this model differed significantly from zero (b=0·31, SE=0·09, p<0·0001). Thus, whether or not microvascular invasion affects survival independently of tumour recurrence, either directly, or by association with other factors, remains to be elucidated.

The model for checking the consistency of outcomes between the individual centres showed that between-centre variability, as estimated from the common random effect, was 22% (SE 8·3): a result indicating that some degree of variation exists, between centres, around an average SMR of 1·18, which indicates a negligible overestimation (<1%) of the model's general predicitive ability with respect to the observed mortality.

Discussion

This study, based on an unprecedented sample size of 1112 patients with hepatocellular carcinomas that fell outside the conventional transplantation criteria, aimed to establish a model that is able to predict survival probabilities on the basis of objective tumour parameters—ie, size of the tumour, number of tumours, and microscopic vascular invasion. The model presented here represents the first large-scale attempt to stratify patients with hepatocellular carcinoma in a continuum of outcome probabilities: an important advance compared with the current dual yes/no approach of the Milan criteria or alternative criteria, which are considered by the transplant community as unduly restrictive.[8–12]

This model provides consistent data for estimates of outcome in most scenarios of liver transplantation for

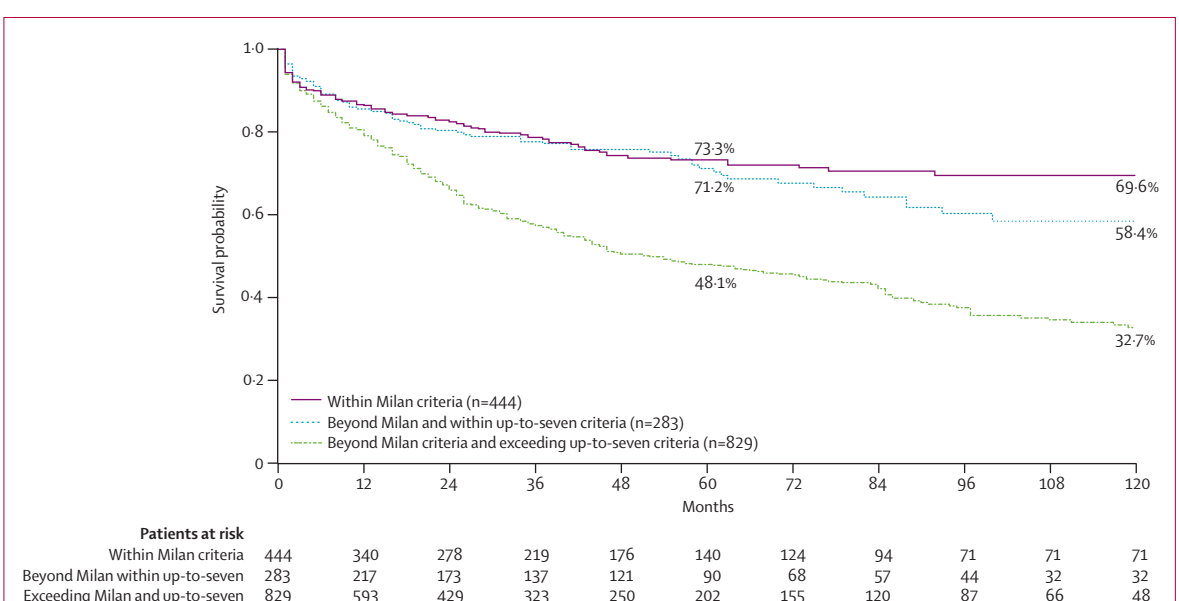

Figure 3: **Up-to-seven criteria**
Kaplan-Meier overall survival curves of the three subgroups: within Milan criteria (n=444); beyond Milan and within up-to-seven criteria (n=283); and beyond Milan and exceeding up-to-seven criteria (n=829). Patients with hepatocellular carcinomas beyond Milan criteria, but within up-to-seven criteria had a similar survival compared with patients within Milan criteria. Patients beyond up-to-seven criteria had a significant deterioration in survival (p<0·001).

hepatocellular carcinoma and identifies three separate prognostic categories: a population fulfilling the so-called up-to-seven rule, in which preoperative assessment of the absence of microvascular invasion is crucial because, in its presence, the results are equivalent to transplantation within conventional criteria (figure 3); an intermediate group (5-year overall survival 50–65%), in which further refinement of prognostication is needed; and a group with characteristics of hepatocellular carcinoma that are associated with such a poor outcome (ie, survival below 50% at 5 years) that transplantation should be considered futile.

After more than a decade of excellent outcomes for liver transplantation for hepatocellular carcinoma with restrictive selection criteria, several expansions of the criteria have been suggested on the basis of post-transplant survival comparable to that achieved after application of the Milan criteria.[10] The lack of consensus on expanded indications has resulted in unreasonable heterogeneity in clinical practice, with some proposals expanded just beyond the borders of the conventional criteria, and others much more liberally dispersed from the conventional limits. In the current scenario, rather than debating whether the expanded criteria are better or worse than the Milan criteria, the fundamental question to be answered is whether expanded criteria can result in post-transplant survival that is considered acceptable to justify the use of a scarce resource.[24,25]

The advantages of an individualised forecast for patients with liver cancer who are proposed for transplant candidacy are self-evident in the frame of graft shortage and limited access to transplantation. However, further refinements of the model are desirable for other parameters that were not included in the present study, such as tumour progression with time, grading, aetiology of cirrhosis (eg, hepatitis B virus or hepatitis C virus), cause of death, response to pre-transplant treatments, alpha-fetoprotein concentrations, and genomic markers,[26–28] which have all been shown to predict outcomes in subgroups of hepatocellular carcinoma, independently from clinical variables.

A second potential limitation of the current model is that data on tumour characteristics were collected from postoperative histopathology reports. It is known that pre-transplant staging fails to predict the number of hepatocellular tumours at pathology in about 25–35% of patients, due to both understaging and overstaging.[29–31] If updated imaging techniques are used, inaccuracies in the pretransplant assessment should not concern the maximum size of the tumour.[32] As for the number of tumours, discrepancies between preoperative and postoperative investigations are currently decreasing with the improving quality of radiological imaging[29,30,32] and can be included in the model by considering alternative scenarios (ie, adding or subtracting one or two tumours in the outcome calculations). Incidentally, this study shows that the importance of the number of tumours decreases as the number increases (figures 1 and 2).

	Milan (within)*	Milan (outside)†	
		Within up-to-seven criteria	Exceeding up-to-seven criteria
Microvascular invasion absent			
Number of patients	361	283	333
Overall survival‡ (95% CI), %			
3 years	81·8 (77·1–85·7)	77·7 (72·0–82·5)	71·8 (66·2–76·7)
5 years	76·1 (70·6–80·7)	71·2 (64·3–77·0)	64·0 (57·7–69·5)
Crude cumulative incidence of recurrence (95% CI), %			
3 years	3·3 (1·8–6·0)	4·8 (2·7–8·6)	17·4 (13·5–22·5)
5 years	3·3 (1·8–6·0)	9·1 (5·6–14·5)	22·3 (17·7–28·0)
Microvascular invasion present			
Number of patients	44	116	338
Overall survival‡ (95% CI), %			
3 years	77·1 (60·2–87·5)	60·2 (49·7–69·2)	41·7 (35·8–47·5)
5 years	71·6 (51·8–84·4)	47·4 (36·4–57·7)	33·0 (27·2–38·9)
Crude cumulative incidence of recurrence (95% CI), %			
3 years	12·8 (5·6–29·6)	31·3 (23·3–41·9)	31·3 (23·3–41·9)
5 years	12·8 (5·6–29·6)	39·9 (30·8–51·7)	51·5 (45·8–57·8)

*Data missing for 39 patients. †Data missing for 42 patients. ‡According to Kaplan-Meier analysis.

Table 3: **Outcome of liver transplantation for hepatocellular carcinoma according to Milan criteria and up-to-seven criteria, in relation to microvascular invasion**

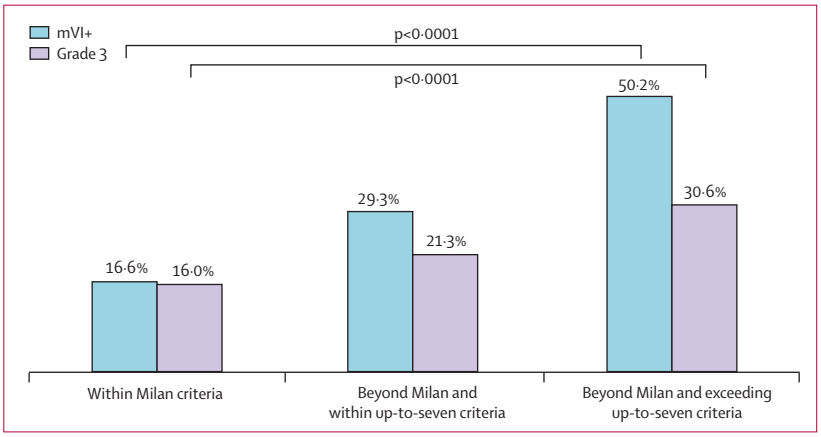

Figure 4: **Correlation of microvascular invasion and poorly differentiated tumour (grade 3) in the identified size-and-number group categories**
In the 1083 patients for whom data on both microvascular invasion and tumour grading were available, a progressive increment of high-grade tumour pattern (grade 3) was noted, which tended to parallel the increase in size-and-number tumour characteristics and the incidence of microvascular invasion (mVI+). By contrast with the other analyses, this analysis included both the presence and absence of microvascular invasion in patients with hepatocellular carcinoma that fell within the up-to-seven criteria. Overall, the chances of detecting an mVI– tumour were significantly higher within the up-to-seven criteria compared with tumours exceeding the proposed limits (70·7% *vs* 49·8%).

For example, if one assumes, in the presented series, a 25% tumour understaging at preoperative imaging with respect to multinodular hepatocellular carcinoma, patients eventually falling within the up-to-seven criteria would have a decrement in 5-year survival from 71% to 65%, namely still within acceptable limits, should

microvascular invasion be confirmed as absent. Such results are in keeping with previous findings[29] and could lead to future adjustments in the counting of tumours for prognostic scores, so that only hypervascular tumours greater than 10 mm in size are included, as per the definition of the Response Evaluation Criteria for Solid Tumours (RECIST).[33]

A limitation in the applicability of the model concerns the information on microvascular invasion, for which only a-priori probabilities or surrogate markers are available preoperatively (ie, alpha-fetoprotein concentrations, response to treatment, and differentiation grade on biopsy). However, microvascular invasion is strictly related to size-and-number covariates and tumour grading, and doubles the hazard of recurrence and death, whichever morphology-related criteria is considered (Milan, up-to-seven, and beyond up-to-seven; table 1 and figure 4). These uncertainties are represented in the confidence intervals of survival probabilities given by the model, and can be integrated in the decision process until future studies will detect reliable preoperative, non-invasive markers of microvascular invasion.

Despite the above-mentioned limitations, our model presents several advantages that are relevant in clinical practice. Above all, it offers individualised survival estimates for a range of tumour configurations and shows that different patients and tumour characteristics can result in the same expected survival (figure 2). Survival estimates, contrary to inclusion or exclusion criteria, allow a more subtle analysis of the benefits of transplantation, such as the estimation of incremental life expectancy as a function of age and of the availability of alternative treatments.[34] Individual survival estimates in patients with hepatocellular carcinoma beyond conventional criteria allow comparison with survival data after other controversial indications to transplantation (ie, hepatorenal syndrome or re-transplantation for hepatitis C infection) that compete with cancer for organ allocation,[35–38] and also allow the consideration of living donation, which, in general, accepts far more liberal patient criteria with deceased donations. In this respect, this study confirmed that post-transplant outcome is strictly dependent on tumour stage rather than graft origin (ie, deceased *vs* living donation).

A further advantage of our study is the robustness of the survival estimates, based on an unprecedented sample size and objective pathological data. This study shows that a group of patients with hepatocellular carcinoma with excellent outcome exists outside the conventional Milan criteria, with upper limits defined by the up-to-seven rule and in the absence of vascular invasion (figure 3). Such limits capture most of the alternative proposals of expansion of conventional criteria (ie, University of California, San Francisco; University of California, Los Angeles; and Tokyo criteria[10,39,40]) and could be the basis for a prospective multicentre investigation.

Finally, a computer-generated estimation of post-transplant prognosis, which takes into account pretransplant staging uncertainties of hepatocelluar carcinoma (ie, tumour number and vascular invasion), could favour an objective approach to the creation of policies and prioritisation for patients with cancer, and could aid clinical decisions according to different scenarios. In fact, clinical-pathological discrepancies, to some extent, depend on patient characteristics and local practices and expertise, and are predictable in individual patients (eg, quality of radiological imaging and range of variations in the pathology variables in clinical practice). The likelihood and the different importance of understaging hepatocellular carcinoma by size versus understaging by number of tumours, as clearly shown by this study (figures 1–3), should also be considered in any computer-generated predictive system.

Until pretransplant assessment of the biological behaviour of hepatocellular carcinoma becomes feasible using molecular techniques or well-tested clinical surrogates, the present model could offer a useful tool for addressing the need to balance patient's expectations and best use of the limited availability of donor organs.

Conflicts of interest

The authors declared no conflicts of interest.

Contributors

V Mazzaferro and P Majno were responsible for the conception and design of the study and for writing the final report. V Mazzaferro, J M Llovet, R Miceli, S Bhoori, M Schiavo, L Mariani, T Camerini, J Bruix, A K Burroughs, and P Majno were involved with the collection and interpretation of data. G L Grazi, L De Carlis, U Cillo, and M Rossi took part in the design of the study. The other authors participated in data management and manuscript review.

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