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Comparison between observed survival after resection of transplantable hepatocellular carcinoma and predicted survival after listing through a Markov model simulation

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Keywords
cirrhosis, hepatic resection, hepatocellular carcinoma, liver transplantation, simulation model.

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Summary

There is still some debate on whether hepatic resection or liver transplantation should be the initial treatment for hepatocellular carcinoma (HCC) in compensated cirrhosis. Clinical data and observed survivals of 150 transplantable patients (within Milan criteria) resected for HCC were reviewed and their predicted survival after listing for liver transplantation was calculated using a Markov model simulation. Differences between observed and predicted survival estimates were explored by standardized differences (d). The mean observed survival within 5 years after surgery was 45.35 months, and the predicted survival after listing was 49.18 months ($d = 0.265$). The largest gain in life-expectancy with liver transplantation would be obtained in patients with Model for End-stage Liver Disease (MELD) score >9 ($d = 0.403$); conversely, observed and predicted survivals were similar in HCV+ patients ($d = -0.002$) and in patients with MELD ≤9 ($d = -0.057$). For T1 tumors, the observed mean estimate of survival after hepatic resection was higher than that predicted by the simulation ($d = -0.606$). In conclusion, in HCV patients and in those with very well compensated cirrhosis, hepatic resection could lead to results similar to those of transplantation strategy for HCC within Milan criteria; HCC T1 patients are probably best served by resection as first-line therapy rather than listing for transplantation.

Introduction

In the last decade, an increasing incidence of hepatocellular carcinoma (HCC) has been observed, and this tumor currently represents the fifth most common cancer and the third most common cause of cancer-related death [1,2]. At present, hepatic resection and liver transplantation are the treatments considered potentially curative. Hepatic resection has the advantage of immediate applicability and no need for spending time on the waiting-list, no need for long-term immunosuppression and a relatively low cost, but the drawback is represented by the high incidence of recurrence that could be expected [3–6]. Despite the high recurrence rate, several different therapies are currently available for patients with tumor relapse that can potentially have a positive impact on survival. In particular, intra-hepatic recurrences can be suitable for potentially curative treatments such as re-resection and salvage liver transplantation. Recent refinements in nonsurgical techniques have also substantially increased the ability of radiofrequency ablation (RFA), percutaneous alcohol injection (PEI), and transarterial chemo-embolization (TACE) to achieve a sustained complete response of target tumors [7,8]; in addition, the introduction of molecular targeted therapies that inhibit tumor proliferation and angiogenesis has opened new prospects in this regard [9]. At the same time, the improvement in diagnostic techniques and in surveillance schedules has led to earlier diagnosis and better accuracy, resulting in increased curability of tumors and, as a result, in more possibilities of survival for patients with a diagnosis of HCC [10–12]. On the other

hand, liver transplantation has the major advantage of curing both HCC and cirrhosis, eliminating the chance of tumor recurrence, and the risk of long-term death from liver failure because of cirrhosis progression; the drawback is represented by the shortage of donor organs that is the major problem in applying primary transplantation to all patients. Liver transplantation must surely be considered as the treatment of choice for HCC in decompensated cirrhosis, but there is some debate on whether hepatic resection or liver transplantation should be the initial treatment for small tumors with compensated cirrhosis.

In the last decade, a large number of cirrhotic patients resected for HCC in our Institution were within Milan criteria, and a considerable proportion of them should be eligible for liver transplantation [13]. What would happen if we decided to list these transplantable patients rather than resect them? As a randomized controlled trial (RCT) seemed to be impossible to perform, we decided to compare the observed survival of HCC patients who underwent hepatic resection with the predicted survival since listing for liver transplantation through a Markov model simulation to define whether the choice of hepatic resection was successful or not.

Methods

Study design

The study was planned to compare patient survival observed after hepatic resection of HCC within Milan criteria with the predicted survival after listing for liver transplantation in an intention-to-treat analysis (Fig. 1). For this purpose, clinical data of all cirrhotic patients who underwent hepatectomy for HCC at the Department of Surgery and Transplantation of the University of Bologna from January 1, 2000 to December 31, 2009, were reviewed. During this time-period, 279 cirrhotic patients underwent hepatic resection. Selection of cases was primarily based on the presence of HCC within Milan criteria (single nodule ≤5 cm or up to three nodules, each of them ≤3 cm, without major vascular invasion or distant metastasis) at preoperative diagnostic techniques [13]; an upper age limit of 70 years was also adopted as an inclusion criterion, as the age limit for liver transplantation is often individualized because it varies with a patient's overall health condition, but it is rare to offer primary transplantation to patients older than 70. Consequently, 52 patients with a tumor outside Milan criteria and 77 patients aged over 70 years were excluded from the study group. The same study population, with identical clinical and tumoral characteristics, was entered in a Monte Carlo micro-simulation of a Markov model built on the basis of literature data or estimated from the United Network for Organ Sharing (UNOS) database to predict survival since listing for liver transplantation.

Patients undergoing hepatic resection

One hundred and fifty cirrhotic patients, undergoing hepatic resection because of the presence of HCC within Milan criteria, were identified with adequate clinical data

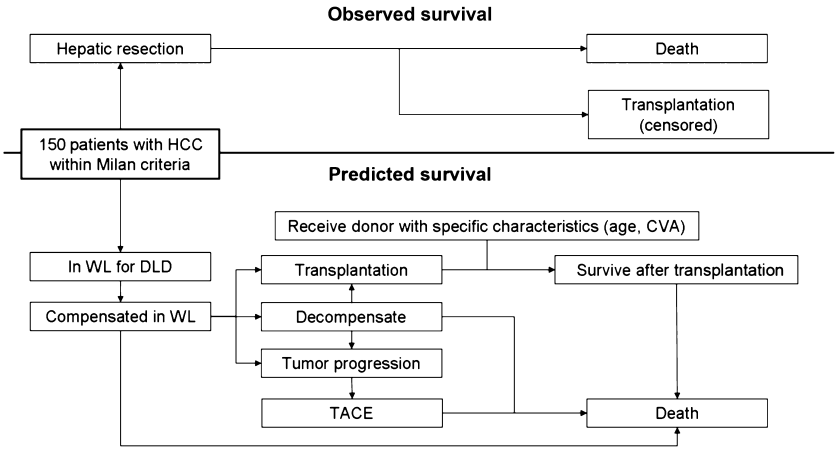

Figure 1 Schematic representation of the study design and the Markov model used in the present analysis. Observed survival was computed from the day of hepatectomy for hepatocellular carcinoma (HCC) within Milan criteria in cirrhotic patients until the most recent follow-up visit or until death, patients who underwent salvage transplantation were censored the day prior to the procedure. Predicted survival was computed since listing for liver transplantation through a Monte Carlo micro-simulation, considering an equal covariate distribution for both the whole study population and for each subgroup considered in the analysis. As the time-horizon of the Markov model was set to 5 years, observed survival over this time limit was censored at 5 years from surgery. WL, waiting-list; DLD, deceased liver donor; CVA, cerebro-vascular accident (as cause of donor death); TACE, trans-arterial chemoembolization.

for review. The policy of our center regarding indications for hepatic resection has already been published: in particular, patients were selected for surgery on the basis of the technical feasibility of success that was established if the residual liver volume was expected to be sufficient after curative resection [14]. In our institution, the presence of esophageal varices, platelet count <100 000/ml^3, and the presence of multiple nodules were not considered exclusion criteria. None of the patients included in the analysis had severe comorbidities that could condition life-expectancy or could represent an absolute contraindication to liver transplantation. The following clinical and biochemical data were collected the day prior to surgery for each patient: age, gender, cause of cirrhosis, serum levels of albumin (g/dl), creatinine (mg/dl), total bilirubin (mg/dl), and international normalized ratio (INR). The Model for End-stage Liver Disease (MELD) score was calculated using the appropriate formula [15]. Age was also categorized on the basis of median value; MELD score was categorized on the basis of both median value of the study population and on the basis of previous published studies [16,17].

Tumors were staged on the basis of preoperative imaging, according to UNOS–TNM classification [18]. The preoperative diagnosis of HCC was based on the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) guidelines [19,20]. Intraoperative ultrasound was performed systematically to detect the presence of any additional nodules not revealed preoperatively and to obtain a tumor-free margin of at least 1 cm; major hepatic resection was defined as the removal of more than two segments: the extent of the hepatectomy was based on the International Hepato-Pancreato-Biliary Association classification [21]. Baseline characteristics of the study population are reported in Table 1.

Table 1. Baseline characteristics of the study population.

Variables	All patients (n = 150)
Age (years)	60.2 ± 7.6
Male gender (%)	121 (80.7)
Hepatitis C positive serology (%)	109 (72.7)
Serum albumin (g/dl)	3.8 ± 0.4
Platelet count (×10^3/mm^3)	125.5 ± 53.3
Serum creatinine (mg/dl)	0.95 ± 0.25
Serum bilirubin (mg/dl)	1.01 ± 0.50
INR	1.17 ± 0.10
Clinical signs of portal hypertension* (%)	62 (41.3)
CTP Score (median; range)	5 (5–8)
Class A (%)	140 (93.3)
Class B (%)	10 (6.7)
MELD Score (median; range)	9 (6–18)
≤9	97 (64.7%)
>9	53 (35.3%)
Preoperative tumor number (median; range)	1 (1–3)
Preoperative solitary tumor	135 (90.0%)
Preoperative size of largest tumor (cm)	3.0 ± 0.9
UNOS–TNM (%)	
T1	16 (10.7)
T2	134 (89.3)
Extension of hepatectomy (%)	
Wedge resection	98 (65.3)
Segmentectomy	33 (22.0)
Bisegmentectomy	19 (12.7)

The preoperative diagnosis of HCC was based upon the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) guidelines.

INR, international normalized ratio; CTP, Child–Turcotte–Pugh; MELD, model for end-stage liver disease; UNOS, United Network for Organ Sharing.

*Defined as (i) esophageal varices detectable by endoscopy or (ii) splenomegaly (major diameter, >12 cm) with a platelet count <100 000/mm^3 according to the Barcelona Clinic Liver Cancer (BCLC) group criteria.

Markov model and Monte Carlo simulation

We built a Markov simulation model (TreeAge Pro 2008; TreeAge Software Inc, Williamstown, MA, USA) that followed the hypothetical cohort of 150 adult cirrhotic patients, with the same clinical and tumor characteristics as the resected population, over 5 years as they moved between different states of health, before and after liver transplantation, and until death (Fig. 1). Calculated variables used in the model during the waiting-list period and after liver transplantation are detailed in Table 2. As 99.3% of resected patients had a MELD score <15 (149 of 150), we assumed an annual mortality rate during the waiting-list period for compensated cirrhosis of 5%, which is consistent with data reported by UNOS for MELD score <15 patients, and the annual decompensation rate assumed was 7%, which is consistent with the probability reported by UNOS to move from MELD score <15 to MELD score ≥15 of 7% per year and within the range of 5–10% per year reported in the literature [22,23]. The annual mortality rate of decompensated patients was assumed to be 20% and within the range of 10–30% reported in the literature [23]. The allocation policy adopted for HCC patients was that proposed by UNOS: briefly, patients with a T1 HCC did not receive extra MELD points, whereas a MELD score of 22 was given to patients with a T2 HCC [24,25]. Patients who dropped out from the waiting-list because of tumor progression were considered as having an intermediate stage HCC (Stage B) according to the Barcelona Clinic Liver Cancer (BCLC) classification [26]. For this group of patients, TACE is the recommended therapy, with a median reported survival of about 20 months [7].

Table 2. Estimates of the values of the variables extracted from the literature and used in the Markov model.

	Base case value	Plausible range	Reference
Variables considered during waiting-list period			
Annual mortality of compensated cirrhosis (%)	5	3–6	[22,23]
Annual decompensation rate (%)	7	5–10	[22,23]
Annual mortality of decompensated cirrhosis (%)	20	10–30	[22,23]
Median time-to-transplant of HCC – T1 (months)	12	1–18	[22,24,25]
Median time-to-transplant of HCC – T2 (months)	2	1–18	[22,24,25]
Monthly drop-out rate of HCC patients (%)	2	1–10	[22,24,25]
Median survival of nonsurgical HCC (months)	20	10–30	[7,26]
Variables considered after liver transplantation			
5-year overall survival after transplantation (%)	70	60–80	[22,24,25]
HR for recipient age >55 years	1.03	NA	[27]
HR for diagnosis = HCV	1.25	NA	[27]
HR for presence of HCC	1.15	NA	[27]
HR for presence of diabetes	1.16	NA	[27]
HR for donor age <18 years	0.89	NA	[27]
HR for donor age 18–39 years	1.00	NA	[27]
HR for donor age 40–49 years	1.16	NA	[27]
HR for donor age 50–59 years	1.35	NA	[27]
HR for donor age ≥60 years	1.44	NA	[27]
HR for donor age ≥60 years in HCV recipient	1.41	NA	[27]
HR for CVA as cause of donor death	1.12	NA	[27]

Annual mortality can be expressed as the reciprocal of life-expectancy: assuming a declining exponential approximation of survival, annual rates can be calculated as $-(\ln S)/t$, where t is the time at which survival S is measured.
HR, hazard ratio; HCC, hepatocellular carcinoma.

After transplantation, the baseline survival at the mean of covariates considered in the present model, for all the recipient population, was about 70%, 5 years after surgery as indicated by the UNOS annual report [18]. Covariate hazard ratios, reported by the Scientific Registry of Transplant Recipients (SRTR), were used in post-transplant mean lifetime prediction; in particular, the following recipient characteristics were considered: age, diagnosis of hepatitis C (HCV), presence of HCC, and diabetes [27]. Regarding the donor characteristics assumed in the present model, the probability of receiving a liver from a donor with specific features is the consequence of the proportion of this feature in the donor pool of the specific geographic area of interest. For this reason, we assumed the distribution of donor age and cause of death, in the same time-period considered, published by our regional share area [28]. Distribution of donor age and cause of death, together with differences with the SRTR [29], are detailed in Fig. 2: it should be noted that donors older than 60 years represent about half of our donor pool. Other donor features, such as anoxia as cause of death, partial/split graft, donation after cardiac death, and African race, were not included in the present model because they are very infrequent in our regional area, as well as in SRTR [28,29]. The hazard ratios reported by the SRTR analysis, related to donor characteristics, were adopted for the post-transplant lifetime prediction [27]; the additional hazard ratio proposed for HCV patients receiving grafts from donors aged 60 years or above was also considered [27]. It should be noted that as the hazard ratios reported by the SRTR-database refer to the absence of the specific condition of interest, we assumed an equal distance from the reported overall survival at the mean of covariates. Consequently, the hazard ratios were corrected according to both the proportion of each specific condition in the study population and the overall survival at the mean of covariates. The model was initially tested to confirm the appropriate fit of the simulation in comparison to the real data reported by the SRTR Annual Report [22,30]. Consequently, waiting-list outcome and post-transplantation survival were simulated on the basis of the distribution of covariates taken into consideration in the present model and reported by the UNOS database. Exploration of the variability and uncertainties of the hypothetical model was performed using one-way and two-way sensitivity analyses.

Statistical analysis

Survival of resected patients (observed survival) was computed from the day of surgery until the most recent follow-up visit or until death; recurrence rate was computed

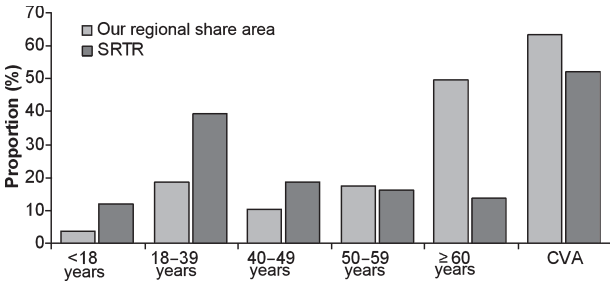

Figure 2 Donor age distribution and prevalence of cerebro-vascular accident (CVA) as cause of donor death in our regional share area and comparison to that reported by the Scientific Registry of Transplant Recipients (SRTR).

from the day of surgery until diagnosis of tumor recurrence. As the time-horizon of the Markov model was set to 5 years, patients surviving over this time limit were censored at 5 years from surgery. In addition, as the purpose of the study was to compare survivals without and with liver transplantation, patients who underwent salvage transplantation were censored the day prior to the procedure. For prediction of survival after listing for liver transplantation (predicted survival), a Monte Carlo micro-simulation was adopted, considering an equal covariate distribution for both the whole study population and for each subgroup considered in the analysis. Mean survival estimates, together with their 95% confidence intervals, were calculated using the Kaplan–Meier method: mean survival time was estimated as the area under the survival curve. Observed survival differences between subgroups were compared with the Log-rank test; conversely, differences between the observed and predicted mean survival estimates were explored by the calculation of standardized differences (d) because of the simulated nature of the comparison. Statistical analysis was performed using SPSS version 10.0 software for PC computer (SPSS, Chicago, IL, USA).

Results

The mean follow-up of the whole study population of 150 patients was 36 months (range, 1 month to 5 years): during this time-period, 48 patients died (32.0%). The most frequent cause of death was tumor recurrence with or without liver failure (23 cases; 47.9%), followed by liver failure without tumor recurrence (22 cases; 45.8%) and other causes that accounted for the remaining proportion (three cases; 6.3%). In particular, after surgery, seven patients developed postoperative liver failure leading to the need for transplantation (four cases) or to patient death (three cases). The 1-, 3-, and 5-year survival rates were 89.3%, 71.6%, and 62.2%, respectively

Table 3. Relationships between variables considered in the Markov model simulation and observed survivals after hepatic resection of cirrhotic patients with hepatocellular carcinoma (HCC) within Milan criteria forming the present study population.

		Observed survival after HR			
Variables	No. of patients	1-year (%)	3-year (%)	5-year (%)	*P*
All patient population	150	89.3	71.6	62.2	
Age (years)					0.203
<62	74	86.3	66.4	59.1	
≥62	76	92.2	76.6	63.0	
Gender					0.238
Male	121	89.2	69.6	59.1	
Female	29	89.4	74.1	64.2	
Hepatitis serology					0.438
HCV positive	109	88.0	70.2	59.2	
HCV negative	41	95.1	75.0	64.6	
Portal hypertension					0.001
Absent	88	96.5	76.7	74.3	
Present	62	80.6	61.6	51.7	
MELD Score					0.007
≤9	97	96.8	77.7	67.6	
>9	53	77.4	60.9	50.4	
Diabetes					0.320
Absent	105	88.4	70.6	56.8	
Present	45	93.3	73.4	67.3	
UNOS–TNM					0.043
T1	16	92.9	82.5	82.5	
T2	134	88.0	69.1	58.4	

MELD, model for end-stage liver disease; UNOS, United Network for Organ Sharing.
Age was categorized on the basis of median value; MELD score was categorized on the basis of both median value of the study population and on the basis of previous published studies [16,17].

(Table 3) corresponding to a mean survival estimated for the resected population of 45.35 months (95% CI = 42.81–47.89). During follow-up, 69 patients experienced tumor recurrence (46.0%): the 1-, 3-, and 5-year recurrence rates were 18.8%, 46.3%, and 63.2%, respectively. In 63 of the 69 recurrent cases (91.3%), the recurrence was confined to the remnant liver, whereas the remaining six also had extra-hepatic lesions (8.7%). In particular, 45 patients presented HCC recurrence within Milan criteria (65.2%). TACE was the first-line therapy most frequently adopted for tumor recurrence, accounting for 46.4% of treatments (32 cases); 18.8% of patients underwent re-resection (13 cases); RFA or PEI was attempted in 11.6% of patients (eight cases); liver transplantation was performed in 8.7% (six cases); systemic chemotherapy or best supportive cares were adopted in 14.5% (10 cases). It should be noted that four patients who were initially treated with TACE or RFA subsequently underwent liver transplantation. At the time of the analysis, another eight

patients who were treated with TACE or RFA or PEI were still on the waiting-list for liver transplantation. Thus, the transplantability rate of recurrence was 26.1% (18 of 69 patients with recurrence). Eight patients, suffering from HCC recurrence within Milan criteria, were not transplanted because they were over the age limit considered for transplantation, with serious comorbidities that had occurred in the meantime.

Considering patient variables included in the lifetime prediction after listing for transplantation of the Markov model, survival after hepatectomy was significantly affected by MELD score ($P = 0.007$) and UNOS–TNM stage ($P = 0.043$) as well as by the presence of clinical signs of portal hypertension ($P = 0.001$), whereas no significant differences were observed within the remaining variables as outlined in Table 3. In particular, survival of patients with MELD score ≤9 was unaffected by the presence of clinical signs of portal hypertension (30 cases of 97; $P = 0.204$); conversely, the presence of portal hypertension had a significant impact on survival of patients with MELD score above 9 (32 cases of 53; $P = 0.005$). The mean survival estimated for patients without clinical signs of portal hypertension and MELD score ≤9 was 51.78 months (95% CI = 47.53–56.02) and 51.35 months (95% CI = 42.94–59.76) when MELD score was above 9 ($P = 0.980$).

Results of the Markov model simulation

The present Markov model was initially tested to explore the correct fit of the simulation on real UNOS data. The simulated drop-out fraction over time was 9.0% at 90 days, 15.7% at 180 days and 28.3% at 1 year since listing, and the 5-year survival rate was 68%. These results are well in keeping with data reported by the UNOS annual report [20,28]: thus, the model appears well calibrated. Table 4 reports mean estimates of observed survival after hepatic resection in comparison to the predicted survival after listing for transplantation originating from the Monte Carlo simulation: in the whole study population of 150 patients, the predicted survival was 49.18 months (95% CI = 47.12–51.24); thus, listing

Table 4. Comparison of observed and predicted survivals using the donor pool from our regional share area.

		Observed survival after HR (months)		Predicted survival since listing (months)		
Variables	No. of patients	Mean estimate	95% CI	Mean estimate	95% CI	*d*
All patient population	150	45.35	42.81–47.89	49.18	47.12–51.24	0.265
Age (years)						
<62	74	44.24	39.05–49.43	49.99	46.00–53.98	0.283
≥62	76	47.23	42.74–51.72	49.00	43.97–54.03	0.083
Gender						
Male	121	45.32	41.46–49.18	48.43	44.97–51.89	0.151
Female	29	49.16	43.31–55.01	49.73	41.96–57.50	0.030
Hepatitis serology						
HCV positive	109	45.33	41.14–49.52	45.29	41.09–48.49	−0.002
HCV negative	41	47.83	41.84–53.82	50.88	45.88–55.88	0.169
Portal hypertension						
Absent	88	51.59	47.76–55.42	50.46	47.12–54.70	−0.037
Present	62	39.04	33.17–44.90	48.59	42.81–54.37	0.408
MELD Score						
≤9	97	50.13	46.49–53.77	48.55	44.96–52.14	−0.087
>9	53	40.52	33.76–47.28	49.38	44.45–54.31	0.403
Diabetes						
Absent	105	45.25	41.04–49.46	48.95	45.48–52.27	0.183
Present	45	48.54	42.49–54.59	49.23	44.19–54.27	0.036
UNOS–TNM						
T1	16	56.47	50.92–62.02	48.09	40.28–55.90	−0.606
T2	134	45.10	41.34–48.86	49.58	45.51–53.65	0.194

For the calculation of predicted survival for each subgroup, proportions of the remaining covariates were assumed identical to those for the observed patients; *d*, standardized differences; *d* values lower than |0.1| indicate very small differences between means; *d* values between |0.1| and |0.3| indicate small differences, *d* values between |0.3| and |0.5| indicate moderate differences and *d* values greater than |0.5| indicate large differences.

MELD, model for end-stage liver disease; UNOS, United Network for Organ Sharing.

for liver transplantation would result in an increase of 3.8 months in 5 years in comparison to hepatic resection ($d = 0.265$). Mean lifetime estimates that should be obtained with listing for transplantation were different in different subgroups: the largest gain in life-expectancy would be achieved in patients with MELD score above 9 ($d = 0.403$) or in the presence of clinical signs of portal hypertension ($d = 0.408$). Of particular interest is the finding that observed and predicted survivals were very similar in HCV positive patients ($d = -0.002$), in patients with MELD scores equal to or less than 9 ($d = -0.057$), and in the absence of portal hypertension ($d = -0.037$). In addition, it should be noted that, in cases of UNOS–TNM T1 tumors, the observed mean estimate of survival after hepatic resection was higher than that predicted by the Monte Carlo simulation ($d = -0.606$). As reported in Fig. 3, in the whole population of the 150 patients, the Markov model was obviously most sensitive to the baseline survival considered (delta = 7.10 months) and to the median time-to-transplant of HCC-T2 tumors (delta = 2.70 months); the annual drop-out rate of all HCC patients and the median survival of nonsurgical HCC (TACE therapy) played a minor role (delta = 1.32 and 1.17 months, respectively), whereas the remaining variables had a minimal impact on the predicted survival of the simulation (delta <1.0 months).

Results from the two-way sensitivity analysis, performed at the simultaneous varying of the median time-to-transplant (*x*-axis) and the 5-year survival after liver transplantation (*y*-axis), are reported in Fig. 4. Of note is the finding that, in the presence of a reduced 5-year post-transplantation survival of 60%, the difference between expected survival since listing and the observed survival after resection ranged between $d = -0.0123$, when the median waiting time was 18 months, and $d = 0.032$, when the median waiting time was 1 month; thus, with respect to a reduced post-transplantation survival, the gain in life-expectancy that could be obtained with listing rather than resection was substantially unaffected by the median time-to-transplant expected. Conversely, with respect to a median waiting time of 1 month (i.e. potential living donor) and an expected 5-year post-transplantation survival up to 80% (i.e. non-HCV patients), a large gain in life-expectancy could be achieved with listing rather than resection ($d = 0.536$).

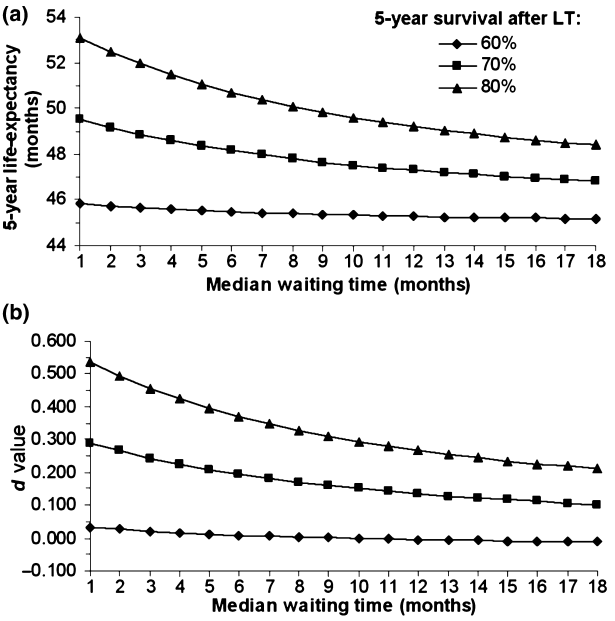

Figure 4 Two-way sensitivity analysis on the variables determining the largest variations in predicted survival after listing for liver transplantation: (a) changes in 5-year life-expectancy in relationship with median time-to-transplant expected (months) and 5-year survival after transplantation; (b) changes in the corresponding distance from observed survival of resected patients reported in standardized differences (*d*).

Discussion

The treatment of HCC patients with cirrhosis is a major challenge. As Milan criteria were established [13], liver

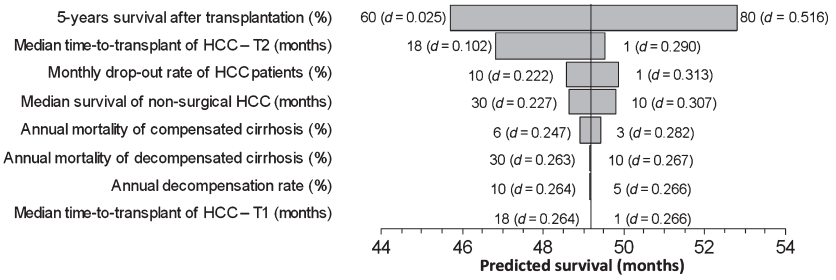

Figure 3 One-way sensitivity analysis on the variables considered in the present Markov model simulation in determining predicted survival after listing for liver transplantation of the whole study population. The distance between predicted survival and observed survival of resected patients was reported in standardized differences (*d*).

transplantation has been considered as the treatment of choice for early HCC in decompensated cirrhosis. Conversely, there is still some debate on whether hepatic resection or liver transplantation should be the initial treatment for small tumors with compensated cirrhosis. Survival after hepatic resection has greatly improved in recent years, mainly as a consequence of refined perioperative care, diagnostic techniques, and follow-up strategies as well as more possibilities of effective treatments for tumor recurrence [5–9]. Several published data showed that, for early HCC, resection can lead to a 5-year survival up to 70% [5,6,31–33]. On the other hand, it should be noted that data from the UNOS annual report and the European Liver Transplant Registry (ELTR) reported that the 5-year survival of transplanted patients with HCC can range between 60% and 70% [22,34]: these results are the consequence of the various donor and recipient factors that can affect survival after transplantation. Thus, what should be the first-line strategy to adopt between resection and listing for transplantation remains to be established.

The results of the present analysis suggest that, in an intention-to-treat analysis, survival after hepatic resection could be very similar to that of liver transplantation since listing. In the whole study population, the gain in life-expectancy, achieved with listing for transplantation rather than resection, was only about 3.8 months over 5 years. This main result is probably the consequence of two features: the high proportion of HCV patients in our study population, and the large proportion of older donors. These two characteristics are well known to be closely related to the outcome after liver transplantation, as older donors have a peculiar, detrimental effect on both hepatitis recurrence and response to antiviral therapy [27,35,36]. It is not surprising that observed and predicted survivals are very similar in HCV patients in the present cohort and the decision to resect or list HCV patients with HCC must probably take into consideration the age of the donor pool available in the geographic share area. In our area, the median donor age is near to 60 years, and so it could be reasonable to resect HCV patients rather than listing them because of the high probability of receiving an older donor; conversely, in areas where the proportion of older donors is less pronounced, like the SRTR area, HCV patients with HCC could probably experience more possibilities of survival with transplantation.

Results from the present study support previous observations that hepatic resection, in patients with more advanced liver disease, namely MELD score above 9, is related to higher postoperative morbidity and mortality [16,17]: In fact, the observed 5-year survival after resection was only 50%, significantly lower than the 70% reported after liver transplantation by UNOS and assumed in the present Markov model. Even if probabilities of tumor progression and death could be expected while on the waiting-list, the possibilities of transplantation overcome these risks, resulting in a net benefit in the intention-to-treat analysis: listing for transplantation would have led to a gain in life-expectancy of 8.9 months over 5 years in these patients. On the contrary, it is of particular interest that observed and predicted survivals were very similar in patients with well compensated cirrhosis: in fact, very good results could be achieved with hepatic resection, where the removal of a limited portion of the liver could result in a residual functioning hepatic volume that is still sufficient [16,17]. Diametrically opposite is the finding that HCC T1 patients would experience a large loss in life-expectancy if listed rather than resected: this is because survival after hepatectomy for small HCC is related to a very good outcome that could be over 70% at 5 years, as already reported by several authors [5,6,31–33]. From a transplantation strategy point of view, this last observation is well in keeping with the UNOS decision to give additional priority points only to candidates with at least stage T2 tumors and to remove additional points from T1 tumors [24].

The results of the present study not only suggest that outcome of hepatic resection could be similar to or even better than that of primary transplantation but also support the potential role of salvage transplantation strategy in the treatment of HCC, as already investigated both in decision analytic contributions [37–39] and subsequent confirmatory series [32,40–43]. HCC patients, within Milan criteria and with preserved liver function, can successfully undergo hepatic resection, limiting the transplantation option to cases of tumor recurrence or hepatic decompensation. In 2000, Majno *et al.*, first reported that this strategy can be considered reasonable [37] and subsequent analysis showed that this strategy is also of benefit for the remaining patients on the waiting-list [39]. Thus, the observation that similar survivals can be obtained with the two surgical strategies considered in the present analysis [41] supports the effort to try to reduce waiting-list size by adopting surgical resection, in a future perspective of salvage transplantation.

Although this is the only study to try to compare observed survival after resection with simulated survival of the same population after primary transplantation, there are some limitations to consider. As with any modeling study, our findings are limited by the quality of the available literature and the assumption of transitional probabilities used in building the model. The optimal analytical way to assess benefit of transplant strategy versus hepatic resection is obviously an RCT that seems to be very hard to propose in a real clinical scenario; at

present, the only way to obtain an estimation of what would happen if we transplant a resectable HCC is simulation models that are based on such assumptions. In addition, there are several other covariates that should be considered in the therapeutic strategy of HCC, namely: the role of ablative techniques [44], the probability of being too old for salvage transplantation, the role of antiviral therapy (especially for HCV patients) after transplantation, or the impact of tumor recurrence after transplantation. In particular, even if according to the UNOS database, the adoption of bridge therapies did not modify removal rates among HCC candidates [30], probably as a consequence of short median time-to-transplant, the response to pretransplant therapies, in clinical scenarios with longer waiting times has been shown able to affect the drop-out from waiting-list [44]. However, there is still little evidence in the literature that allows bridge therapy to be included as a variable in the simulation model and the introduction of this and other features probably really increases the complexity of a Markov analysis while adding relatively little to the accuracy of the present outcome (MM Abecassis, personal communication, http://74.43.177.57/courses/2010/sal/abecassis/player.html).

In conclusion, in HCV patients and in those with very well compensated cirrhosis, hepatic resection could lead to results similar to those of transplantation strategy for HCC within Milan criteria; in HCV positive patients, the choice of the optimal strategy to adopt must be based on age of the donor pool available in the geographic area of interest, as older donor age has a detrimental effect on HCV recurrence. HCC T1 patients are probably best served by resection as first-line therapy rather than listing for transplantation.

Authorship

AC: designed the study and analyzed data. MC and GE: wrote the paper. MCM and ADP: provided important intellectual contribution and results interpretation. MDG and MZ: collected data and helped in analyze data.

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