American Journal of Transplantation 2010; 10: 619–627
Wiley Periodicals Inc.

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doi: 10.1111/j.1600-6143.2009.02984.x

Harm and Benefits of Primary Liver Resection and Salvage Transplantation for Hepatocellular Carcinoma

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Primary transplantation offers longer life-expectancy in comparison to hepatic resection (HR) for hepatocellular carcinoma (HCC) followed by salvage transplantation; however, livers not used for primary transplantation can be reallocated to the remaining waiting-list patients, thus, the harm caused to resected patients could be balanced, or outweighed, by the benefit obtained from reallocation of livers originating from HCC patients first being resected. A Markov model was developed to investigate this issue based on literature data or estimated from the United Network for Organ Sharing database. Markov model shows that primary transplantation offers longer life-expectancy in comparison to HR and salvage transplantation if 5-year posttransplant survival remains higher than 60%. The balance between the harm for resected patients and the benefit for the remaining waiting list depends on (a) the proportion of HCC candidates, (b) the percentage shifted to HR and (c) the median expected time-to-transplant. Faced with a low proportion of HCC candidates, the harm caused to resected patients was higher than the benefit that could be obtained for the waiting-list population from re-allocation of extra livers. An increased proportion of HCC candidates and/or an increased median time-to-transplant could lead to a benefit for waiting-list patients that outweighs this harm.

Key words: Hepatic resection, hepatocellular carcinoma, life-expectancy, liver transplantation, organ allocation

Received 04 September 2009, revised 22 October 2009 and accepted for publication 08 November 2009

Introduction

Hepatocellular carcinoma (HCC) represents one of the most common tumors worldwide, and its incidence is increasing in western countries (1,2). Two therapies are currently considered as potentially curative: hepatic resection (HR) and liver transplantation (LT). LT should be considered as the optimal strategy because it removes not only the tumor but also the underlying cirrhotic liver that is at risk for the development of *de novo* HCC; however, the shortage of donor organs represents the major problem in applying primary transplantation to all patients. HR remains an important therapeutic option but the long-term prognosis is undermined by a high incidence of HCC recurrence, up to 50–70% of cases 5 years after surgery. The combination of both treatments can be a reasonable strategy: HCC patients, within Milan criteria (3) (single nodule $\leq$5 cm or two or three nodules $<$3 cm) and with preserved liver function, can successfully undergo HR, limiting the transplantation option to cases of tumor recurrence or hepatic decompensation. In 2000, Majno et al. reported that this strategy, called salvage transplantation, can be considered reasonable; nevertheless, considering a median time-to-transplant of 6 months, and a monthly waiting list drop-out rate of 3%, primary transplantation proved the best strategy to adopt, providing a longer life-expectancy in comparison to HR and salvage transplantation (4).

During the last decade, the clinical scenario has substantially changed. Significant improvements in the surveillance of cirrhotic patients (5,6) and those in postoperative care (7,8) have led to a significant improvement of survival after resection; on the other hand, the allocation policy for LT has moved from a Child–Turcotte–Pugh (CTP) based allocation system to the more accurate model for end-stage liver disease (MELD) system, reducing waiting list mortality (9,10). The new liver allocation policy proposed by the United Network for Organ Sharing (UNOS) assigns priority to HCC patients on the basis of their risk of becoming ineligible for transplantation: this policy initially led to a significant reduction of the waiting list drop-out rate from 25.9% in the pre-MELD era to 6.7% in the post-MELD era (9), resulting in an actual median time-to-transplant for HCC patients of 3 months (11,12) and a monthly drop-out rate of about 2% (10,12). Even faced with an increased curability of HCC by HR, it seems that there is no role for salvage transplantation with the present allocation policy. However, faced with the chronic shortage of donors, livers

not used for primary transplantation can be reallocated to the remaining waiting-list patients: can the harm caused to HCC patients, submitted to HR and salvage transplantation, be balanced, or even outweighed, by the benefit obtained for the rest of the candidates?The aim of the present study was to develop a Markov simulation model to: (a) compare, across the pre- and posttransplant periods (intention-to-treat analysis), the life-expectancy of patients undergoing primary HR and salvage transplantation versus primary LT under the new MELD allocation policy and (b) measure the harm and benefits of the salvage transplantation strategy in patients submitted to HR and in the remaining waiting-list population (gain in life-expectancy). The adoption of this model allows complex simulations of multistate transitions between various health conditions, at different rates, and over an extended period of time, and makes it possible to perform a sensitivity analysis that could be used to identify important clinical variables that influence the overall outcome of the simulation, and, thus, the best strategy to adopt.

Patients and Methods

Decision analytical model

We built a Markov simulation model using TreeAge Pro 2008 (TreeAge Software Inc., Williamstown, MA) that follows a hypothetical cohort of adult cirrhotic patients, with an average age of 55 years, over 10 years as they moved between different states of health, before and after LT, until death. Patients with HCC were divided into two groups: patients submitted to HR followed by salvage transplantation, in the case of tumor recurrence or hepatic decompensation, and patients listed for primary transplantation; this separation was necessary to analyze the life-expectancy associated with each strategy. A control group of cirrhotic patients, without HCC and listed for primary transplantation, was also taken in consideration to analyze the benefit originating from the reallocation of organs that derive from moving HCC patients from the waiting list to HR. Patients needing retransplantation, or transplantation for causes different from cirrhosis or HCC, were excluded from the simulation.

All HCC patients began the simulation with a diagnosis of HCC within Milan criteria (3) (single nodule ≤5 cm or two or three nodules <3 cm, without tumoral invasion of the portal or hepatic veins, and no extrahepatic spread of the tumor) and preserved liver function (CTP Class A). Patients could receive HR as the first line treatment, or could be placed on the waiting list for primary transplantation from deceased liver donors (Figure 1). Patients receiving hepatectomy could die from surgery, decompensate or survive. Survivor patients were followed under a semiannual or annual surveillance and could decompensate, die and/or experience tumor recurrence. Decompensated patients, and those who experienced tumor recurrence within Milan criteria, were promptly placed on the waiting list for salvage transplantation from deceased liver donors; thus, probabilities of transplantation or death were those of waiting-list candidates. Patients who experienced a tumor recurrence out of Milan criteria were considered to have a nonsurgical recurrence and were submitted to transarterial chemoembolization (TACE). HCC patients placed on the waiting list for salvage transplantation, as well as those listed for primary transplantation, could decompensate, be transplanted, die from cirrhosis-related complications or develop tumor-related complications, such as tumor growth, a condition that dropped patients off the waiting list, placing them in the TACE treatment group. The allocation policy adopted for HCC patients was the one proposed by the UNOS: briefly, patients with a T1 HCC (single nodule less than 2 cm) did not receive extra-MELD points whereas a MELD score of 22 was given to patients with a T2 HCC (single nodule of 2–5 cm or two or three nodules none larger than 3 cm) (13,14). We considered intrahepatic recurrence as a T2 recurrence.

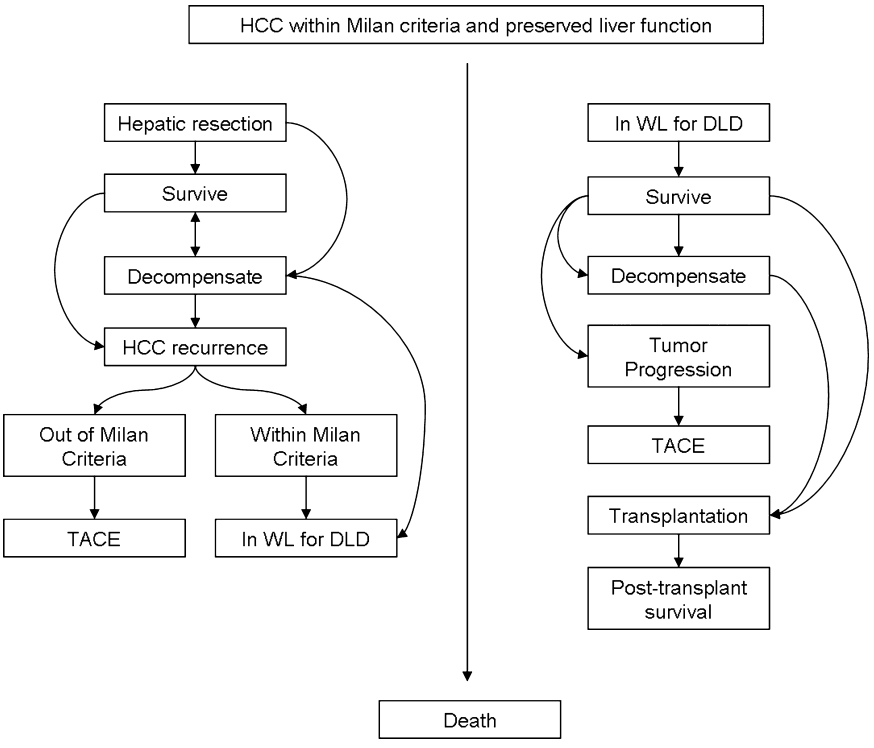

Figure 1: Schematic diagrams of the Markov model for the decision to submit a cirrhotic patient with HCC within Milan criteria and preserved liver function to hepatic resection or to enter the waiting list (WL) for a deceased liver donor (DLD). In the case of tumor recurrence or progression out of Milan criteria, patients were considered as having an intermediate HCC and were submitted to transarterial chemoembolization (TACE). All health states can proceed directly to death, arrows are omitted for simplicity.

Table 1: Estimates of the values of the variables extracted from the literature and used in the analysis. Annual mortality can be expressed as the reciprocal of life-expectancy: assuming a declining exponential approximation of survival, annual rates can be calculated as–(lnS)/t, where t is the time at which survival S is measured

	Base case value	Plausible range	References
Variables considered after hepatic resection			
Postoperative mortality	0.03	0.01–0.06	8,20–22
Postresection decompensation rate	0.04	0.02–0.06	8,20,21
Annual mortality of compensated cirrhosis (MELD <15)	0.05	0.03–0.06	12,23
Annual decompensation rate (MELD ≥ 15)	0.07	0.05–0.10	12,23
Annual incidence of HCC recurrence	0.20	0.15–0.25	20,24,25,28
Probability of HCC recurrence within Milan criteria	60%	23–89%	20,22,27–30
Variables considered while on the waiting list			
Proportion of list with HCC	10%	5–15%	11,12,15,31
Proportion of list with MELD 15–22	30%	25–35%	12,15
Proportion of list with MELD 23–30	15%	10–20%	12,15
Proportion of list with MELD >30	8%	5–10%	12,15
Annual drop-out rate of HCC patients	0.02	0.01–0.10	10,11,15
Annual mortality of listed patients with MELD 15–22	0.14	0.12–0.17	12,15
Annual mortality of listed patients with MELD 23–30	0.19	0.17–0.22	12,15
Annual mortality of listed patients with MELD >30	0.28	0.26–0.30	12,15
Annual transplant rate of HCC patients	0.70	0.68–0.72	12
Annual transplant rate of MELD 15–22	0.50	0.37–0.63	12,15
Annual transplant rate of MELD 23–30	0.65	0.50–0.80	12,15
Annual transplant rate of MELD >30	0.60	0.45–0.75	12,15
Other variables considered			
5-years survival after transplantation	70%	60–80%	12
Overall annual mortality of nonsurgical HCC	0.45	0.27–0.63	36–38

Non-HCC patients on the waiting list for primary transplantation were stratified according to their MELD score at listing as follows: MELD 15–22; MELD 23–30 and MELD >30; we excluded from the analysis patients without HCC having a MELD score below 15, because recent reports suggest that the survival benefit of transplantation is uncertain in these patients (15–17). Similarly to HCC patients on the waiting list, these patients could move to another MELD score category, be transplanted, die from cirrhosis-related complications or develop a *de novo* HCC and/or tumor-related complications, a condition that dropped patients off the waiting list, placing them in the TACE treatment group.

Data Sources

The variable estimates used in the present Markov model were extracted from articles published in the last decade searched in the MEDLINE database and from data reported on the Web sites of the Organ Procurement and Transplantation Network (12). No language exclusion criteria were applied during the literature search. Appraisal of all the pertinent studies was graded by their level of evidence (18); when available, estimates were extracted from randomized controlled trials and, if missing, from quasi-randomized trials, prospective cohort studies, retrospective cohort studies, and case series in the above order. Probabilities were calculated following the DEALE method (19) according to the formula (lnS)/t where t is the time at which the survival S is measured; plausible ranges were extracted from the literature or calculated according to the beta-distribution assumption (95% confidence interval). The summary of probabilities and ranges extracted and used in the present Markov model is reported in Table 1.

Variables considered after HR

The outcome of partial hepatectomy in cirrhotic patients has improved remarkably in recent years with improved surgical techniques and perioperative care (7,8): mortality is reported to range between 0% and 5% in tertiary centers and postoperative hepatic decompensation to be about 4% (8,20–22). The annual mortality rate assumed was 5%, which is consistent with data reported for CTP Class A patients of 1-year survival of about 95% (23) and with data reported by OPTN for MELD <15 patients (12). The assumed annual decompensation rate from CTP Class A to CTP Class B/C was 7%, which is consistent with the probability reported by OPTN to move from MELD <15 to MELD ≥15 of 7% per year (12) and within the range of 5–10% per year reported in the literature (23). The rate of HCC recurrence after HR varies according to the characteristics of the resected tumor and the presence of underlying cirrhosis. The annual recurrence rate, used in the present Markov model, was extracted only from series regarding cirrhotic patients, undergoing partial hepatectomy and having HCC within Milan criteria. On the basis of these criteria, the baseline annual recurrence rate assumed was 20% per year (20,24–26). Regarding transplantability of HCC recurrence, the literature reports that tumor recurrence suitable for salvage transplantation occurs with a median of 60%, ranging from 23% to 89% (20,22,27–30).

Variables considered during the waiting list period and after transplantation

Calculated variables used in the model during the waiting list period are detailed in Table 1 and are comparable to those used in previously published models of the liver transplant organ allocation system (11,12,15,31,32). Regarding survival after transplantation, we assumed that the procedure-related mortality of salvage transplantation was the same as that of primary transplantation, as recently reported (28,29,33); in addition, the same posttransplantation survival rates were used for all waiting-list patients, as these do not vary substantially by MELD score (16,17) and it is unclear whether MELD score could predict posttransplantation survival over the long-term (34).

Survival of HCC patients not suitable for LT

We considered HCC patients not suitable for LT as having an intermediate stage HCC (Stage B) according to the Barcelona Clinic Liver Cancer classification (35). For this group of patients, TACE is the recommended

therapy to adopt, with a median reported survival of about 20 months (36–38).

Sensitivity analysis and reallocation simulation

Exploration of the variability and uncertainties of the hypothetical model was performed by sensitivity analysis. One-way sensitivity analysis was performed to explore the effects on the best strategy by varying the value of each single estimate over a range while the other parameters remained constant; the effect of simultaneous changes in two estimates was evaluated using two-way sensitivity analysis. The reallocation policy simulated that livers originating from moving HCC patients from the waiting list to HR were proportionally distributed to non-HCC patients, and to remaining HCC patients, on the basis of the proportion of HCC patients in the entire waiting-list population and the transplant probability of each group: if HCC represents 10% of all candidates, moving half of them to HR will result in an increased liver availability across the entire population of $0.1 \times 0.5 = 5\%$; considering a transplant probability of a specific group of 50% the increment will be $0.5 \times 0.05 = 2.5\%$, resulting in a new probability of being transplanted for 52.5% of this group.

Results

On an intention-to-treat basis, the Markov model showed that, with the UNOS policy of liver allocation to HCC patients, primary transplantation gives a longer life-expectancy in comparison to HR and salvage transplantation: 10 years since intention-to-treat, the calculated life-expectancy for patients undergoing primary transplantation was 6.78 years, and for patients undergoing HR was 6.20 years (Figure 2A); thus, the gain in life-expectancy obtained with primary transplantation was 0.58 years, which corresponds to about 7 months. Regarding graft use, 76.9% of listed patients received LT, whereas only 28.3% of patients submitted to HR received salvage transplantation. Differences in grafts used between the two treatment groups reached a maximum of 63.3% in the first year since intention-to-treat (Figure 2B). Patients listed for primary transplantation experienced a tumor progression that

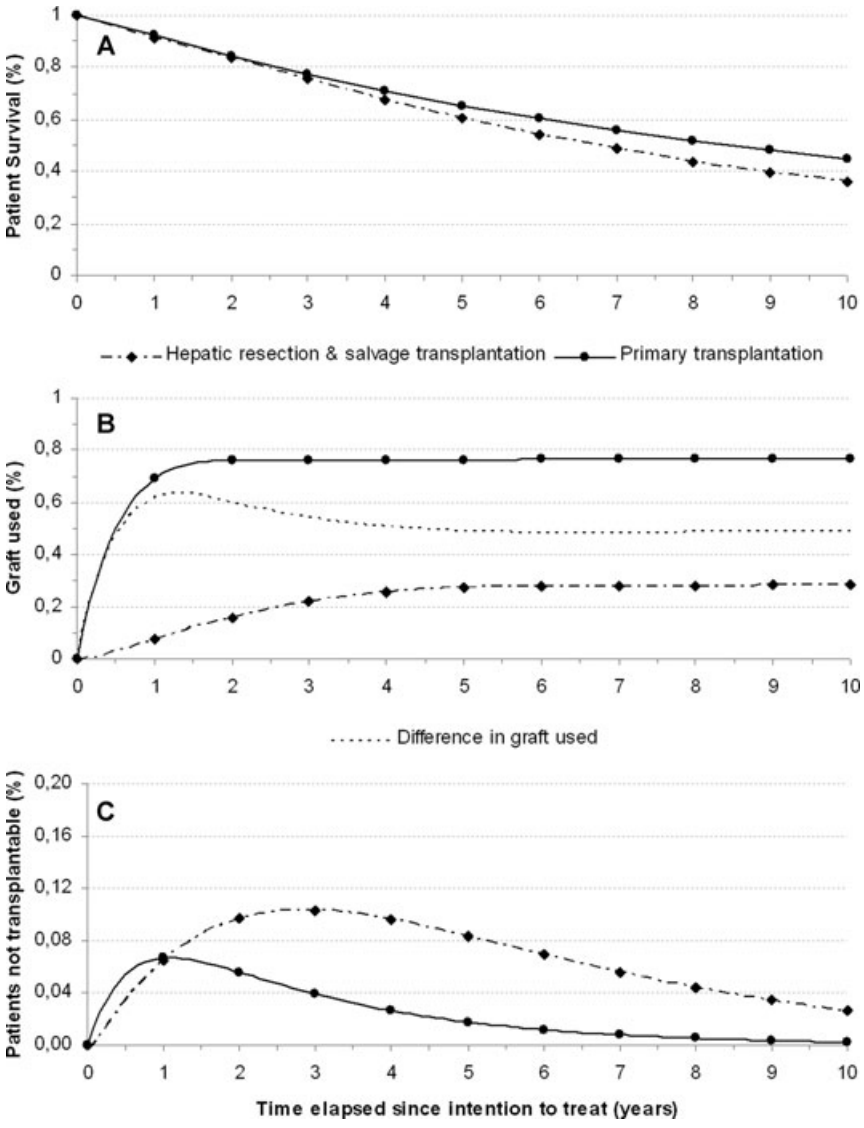

Figure 2: (A) Intention-to-treat analysis resulting the from Markov model that compares patients receiving hepatic resection and salvage transplantation for tumor recurrence or decompensation versus primary transplantation; (B) transplant rate of patients undergoing salvage transplantation versus primary transplantation and (C) dropout rate of patients undergoing salvage transplantation versus primary transplantation.

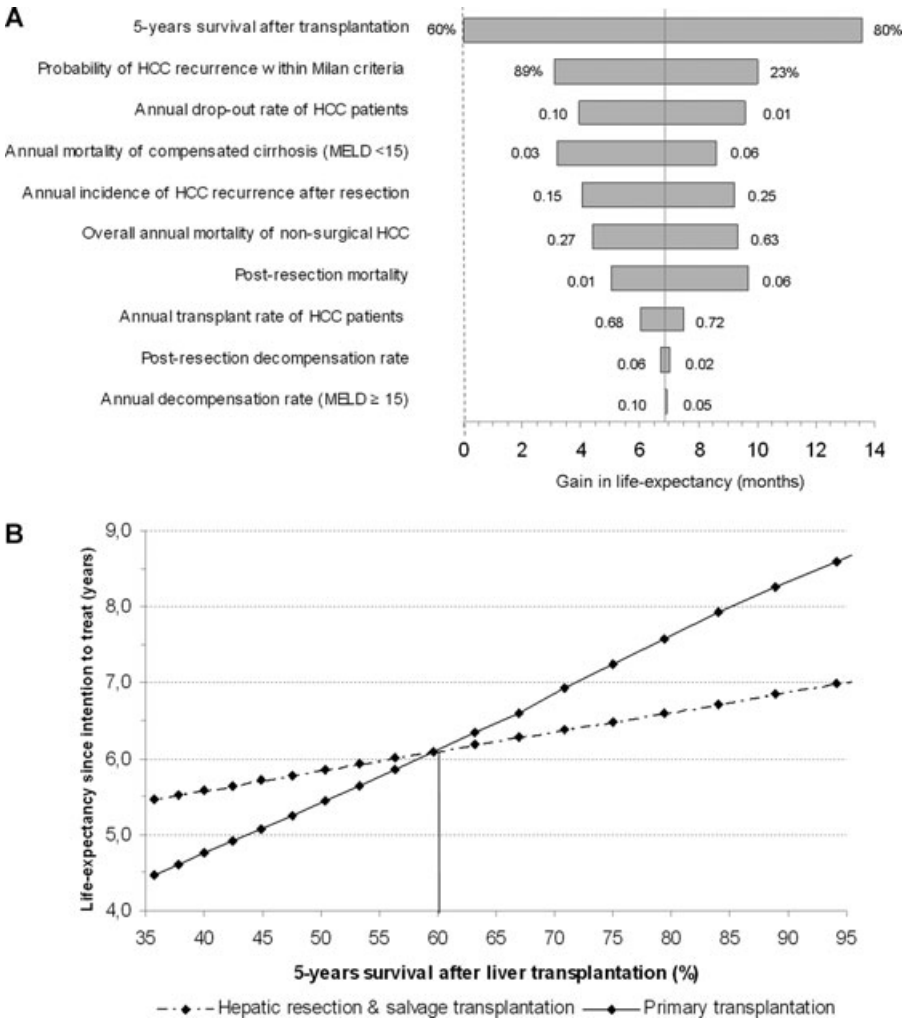

Figure 3: (A) Tornado diagram showing the gain in life-expectancy (in months) obtained with primary transplantation in comparison to hepatic resection and salvage transplantation on variation of the parameters considered in the analysis. (B) One-way sensitivity analysis showing that primary transplantation was no longer the best strategy to adopt faced with a 5-year posttransplantation survival lower than 60%.

led to a drop-out rate from the waiting list of 6.6% in the first year after listing and then decreased; whereas a larger proportion of resected patients developed recurrence or tumor progression that led to nontransplantability with a maximum of 10% 3 years after HR and then decreased (Figure 2C). Sensitivity analysis showed that none of the variables used in the present model modified the results within their respective plausible ranges considered, except for annual mortality rate after transplantation (Figure 3A): in fact, HR became the best strategy to adopt if the 5-year survival rate after LT was lower than 60% (Figure 3B). Simulations for different age populations and two-way sensitivity analysis did not change the overall results.

Figure 4 reports the thresholds required to obtain a balance between the harm caused to resected patients and the benefit (gain in life-expectancy) obtained from reallocation of livers to the remaining waiting-list patients. In the base-case scenario, with a proportion of HCC candidates of 10% and a median time-to-transplant of 3 months, the percentage of patients to be resected was higher than 100% and thus not possible to achieve (Figure 4A). However, faced with an increased proportion of HCC patients on the waiting list and/or an increased median time-to-transplant, HR and salvage transplantation could produce a gain in life-expectancy for the waiting-list population that outweighs the harm caused to resected patients. Considering, for example, a proportion of HCC candidates of 30% and a median time-to-transplant of 6 months, submitting 35% of these patients to HR resulted in a balance between harm and benefit for the remaining waiting-list candidates (Figure 4A); if the median time-to-transplant increases to 12 months, the proportion of patients to be submitted to HR decreases to 18% (Figure 4A). Over the thresholds reported in Figure 4A, gain in life-expectancy for waiting-list patients increased proportionally to the percentage of patients submitted to HR. As already reported, in the base-case scenario, the increase of this percentage did not achieve any benefit for waiting-list candidates (Figure 4B); on the contrary, faced with a proportion of HCC candidates

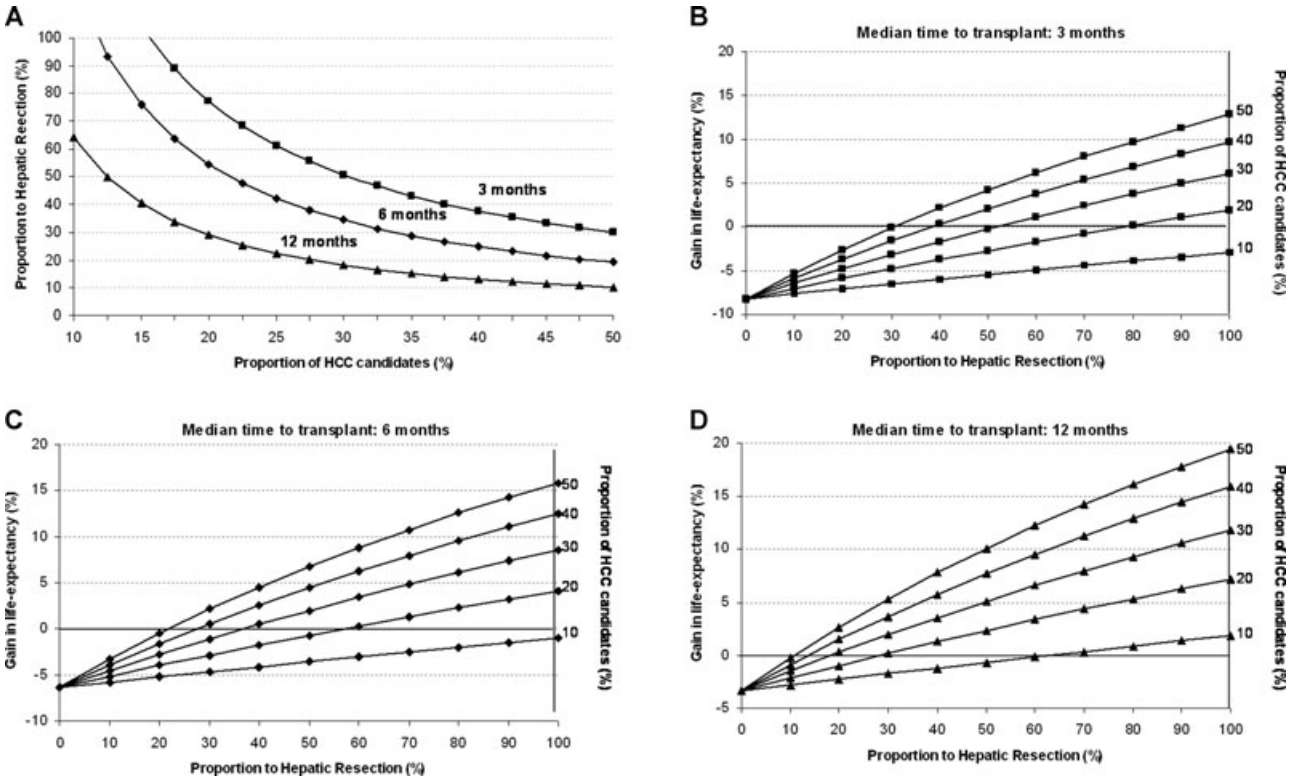

Figure 4: Simulation of reallocation of livers originating from the salvage strategy: (A) thresholds required to obtain a balance between harm caused to resected patients and gain in life-expectancy for the remaining waiting-list population; (B) relationship between the gain in life-expectancy and the proportion of HCC patients on the waiting list and the percentage moved to hepatic resection considering a median time-to-transplant of 3 months; (C) median time-to-transplant of 6 months and (D) median time-to-transplant of 12 months.

of 30% and a median time-to-transplant of 6 months, the gain in life-expectancy for waiting-list candidates progressively increased (Figure 4C) and was more pronounced if median time-to-transplant was 12 months (Figure 4D).

Discussion

HR and LT are now largely considered as complementary, not competitive, treatments for HCC in cirrhotic patients with well-preserved liver function. HR outcome is mainly influenced by a high rate of tumor recurrence that limits long-term results, whereas LT applicability is limited by the shortage of liver donors. In such a clinical scenario, the concept of salvage transplantation can be considered a reasonable strategy that can partially solve both problems. The present analysis showed that under the current UNOS allocation policy, life-expectancy of primary transplantation was longer than that of HR followed by salvage transplantation; however, the gain in life-expectancy obtained by primary transplantation was quite small (about 7 months over 10 years since intention-to-treat). On the contrary, the strategy of salvage transplantation led to an increased pool of livers, originating from HCC patients first being resected, of about 50% of the HCC population over 10 years that could be reallocated, but can the harm caused to patients submitted to HR be overtaken by the benefit obtained as a result of liver reallocation? At present, the expected benefit is related to: (a) the proportion of HCC patients on the waiting list; (b) the proportion of patients that could be moved to HR and (c) the median time-to-transplant as a result of the allocation policy of HCC patients. In the United States, the proportion of HCC patients on the waiting list is about 10% and the median time-to-transplant is 3 months (11,12): in such a clinical scenario, there is probably no role for salvage transplantation because of the low proportion of livers that will originate from this strategy. The low proportion of HCC patients on the waiting list probably reflects the low tumor incidence in the United States (39) or is already the result of a shift to HR of HCC patients rather than LT, but in countries where HCC incidence is higher, an increased proportion of HCC patients on the waiting list can be expected. Studies from southern European countries reported a prevalence of HCC patients on the waiting list of about 30% (39–42): in such a clinical scenario, moving at least half of HCC patients from primary transplantation to

HR resulted in a gain in life-expectancy for waiting-list patients that exceeded the harm caused to resected patients. In addition, allocation policies for HCC patients could differ among transplant centers, leading to an increased median time-to-transplant: our model showed that the higher the median time-to-transplant, the lower the proportion of HCC patients needed to obtain a benefit for the waiting-list population; considering that the current literature reports a proportion of HCC patients that could be candidates for both HR and transplantation that ranges from 20.4% to 50.1% (29–33), this policy could be followed. It must also be considered that recent evidence has shown an increase of HCC incidence in western countries due to the epidemic of hepatitis C (39); in addition, the improved surveillance of cirrhotic patients has led to diagnosis of HCC at earlier stages, submitting more patients to potentially curative treatments such as LT (5,6). Thus, an increasing proportion of HCC patients on the waiting list has to be expected and salvage transplantation would be a reasonable strategy if the chronic shortage of donors persists.

In the present analysis, we found that the only determinant of the best strategy to adopt, within the plausible ranges considered, was survival after transplantation. A 5-year survival of 60% was found to be the threshold for strategy change: if 5-year survival after transplantation was lower than this threshold, HR and salvage transplantation became the best strategy to adopt. This aspect is particularly important in the setting of transplantation of HCC exceeding Milan criteria. Among all HCC patients, up to 70% are diagnosed at advanced stages of the disease (6), and are not suitable candidates for transplantation by Milan criteria. This situation has led some authors to call for awarding priority MELD points to patients with tumors exceeding Milan criteria. Yao et al. (43) proposed a new set of criteria, the University of California at San Francisco (UCSF) criteria: a solitary tumor of 6.5 cm or less, no more than three lesions with the largest being 4.5 cm or less, and a total tumor diameter 8 cm or less, without gross vascular invasion. Five-year survival rates for these patients have been reported to range between 38% and 93%, but what proportion of UCSF patients would have to survive 5 years after transplantation in order to justify these extended criteria (11)? Results from Volk et al. (11) showed that expanding Milan criteria would require a 5-year posttransplantation survival of at least 61% to outweigh the harm caused to other patients on the waiting list. Interestingly, 60% was the threshold obtained from our model to submit a patient to HR rather than primary transplantation. Taking these observations together, the conclusion should be that, with a posttransplantation 5-year survival lower than 60%, HCC patients exceeding Milan criteria not only should not be transplanted because of the harm caused to the other candidates, but also that HR, if feasible, and salvage transplantation, is the best strategy to adopt.

While this is the only study to address the harm of salvage transplantation and the benefits obtained from liver reallocation, there are some limitations to consider. First, the present study ignores the effect of retransplantation and assumes the same posttransplantation survival regardless of MELD: these two features can potentially modify transplant probabilities and can decrease the posttransplantation survival. Second, it did not take into account HCC patients receiving exception points so that these patients were excluded from the reallocation simulation. However, transplant probabilities and posttransplantation survival obtained from the UNOS annual report are most likely to be already affected by the presence of retransplantation and MELD exception and it is unclear whether MELD score could predict posttransplantation survival over the long-term (16,17,34). More detailed studies, focused on the effect of retransplantation, of different posttransplantation survival rates and considering the benefits obtained for MELD exception patients are warranted. Finally, as with any modeling study our findings are limited by the quality of the available literature.

In conclusion, under the current policy of liver allocation for HCC patients, salvage transplantation seems to offer no advantages in comparison to primary transplantation in countries with a low proportion of HCC patients on the waiting list; however, the loss in life-expectancy is quite small and could be balanced or outweighed by the benefit to the remaining waiting-list patients. In countries with a higher incidence of HCC, a higher proportion of HCC patients on the waiting list and/or a longer median time-to-transplant, salvage transplantation could offer a gain in life-expectancy to the remaining waiting-list patients. If 5-year survival after LT decreases below 60%, HR, when feasible, should be considered as the best strategy to adopt.

Acknowledgments

Funding sources: None to declare. Thanks to Ms. Susan West for writing assistance.

References

1. El-Serag HB, Davila JA, Petersen NJ, McGlynnn. The continuing increase in the incidence of hepatocellular carcinoma in the United States: An update. Ann Intern Med 2003; 139: 817–823.
2. Thompson Coon J, Rogers G, Hewson P et al. Surveillance of cirrhosis for hepatocellular carcinoma: Systematic review and economic analysis. Health Technol Assess 2007; 11: 1–206.
3. Mazzaferro V, Regalia E, Doci R et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996; 334: 693–699.
4. Majno PE, Sarasin FP, Mentha G, Hadengue A. Primary liver resection and salvage transplantation or primary liver transplantation in patients with single, small hepatocellular carcinoma and preserved liver function: An outcome-oriented decision analysis. Hepatology 2000; 31: 899–906.
5. Sherman M. Screening for hepatocellular carcinoma. Hepatol Res 2007; 37 (S2): S152–S165.

6. Trevisani F, De Notaris S, Rapaccini G et al.; Italian Liver Cancer Group. Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: Effects on cancer stage and patient survival (Italian experience). Am J Gastroenterol 2002; 97: 734–744.
7. Grazi GL, Ercolani G, Pierangeli F et al. Improved results of liver resection for hepatocellular carcinoma on cirrhosis give the procedure added value. Ann Surg 2001; 234: 71–78.
8. Imamura H, Seyama Y, Kokudo N et al. One thousand fifty-six hepatectomies without mortality in 8 years. Arch Surg 2003; 138: 1198–1206.
9. Wiesner RH, Freeman RB, Mulligan DC. Liver transplantation for hepatocellular cancer: The impact of the MELD allocation policy. Gastroenterology 2004; 127(S1): S261–S267.
10. Sharma P, Harper AM, Hernandez JL et al. Reduced priority MELD score for hepatocellular carcinoma does not adversely impact candidate survival awaiting liver transplantation. Am J Transplant 2006; 6: 1957–1962.
11. Volk ML, Vijan S, Marrero JA. A novel model measuring the harm of transplanting hepatocellular carcinoma exceeding Milan criteria. Am J Transplant 2008; 8: 839–846.
12. OPTN. 2007 Annual Report. Available from: www.optn.org/data/annualReport.asp. Accessed June 15, 2009.
13. Freeman RB, Mithoefer A, Ruthazer R et al. Optimizing staging for hepatocellular carcinoma before liver transplantation: A retrospective analysis of the UNOS/OPTN database. Liver Transpl 2006; 12: 1504–1511.
14. UNOS/OPTN. Modifications to policy 3.6.4.4 (Liver candidates with hepatocellular carcinoma). 3.6. Allocation of Livers. Last access on 01 July 2009. Available at: http://www.unos.org/PoliciesandBylaws2/policies/docs/policy 8.doc.
15. Perkins JD, Halldorson JB, Bakthavatsalam R, Fix OK, Carithers RL Jr, Reyes JD. Should liver transplantation in patients with model for end-stage liver disease scores <or = 14 be avoided? A decision analysis approach. Liver Transpl 2009; 15: 242–254.
16. Merion RM, Schaubel DE, Dykstra DM, Freeman RB, Port FK, Wolfe RA. The survival benefit of liver transplantation. Am J Transplant 2005; 5: 307–313.
17. Schaubel DE, Guidinger MK, Biggins SW et al. Survival benefit-based deceased-donor liver allocation. Am J Transplant 2009; 9: 970–981.
18. Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ. Users' guides to the medical literature. IX. A method for grading health care recommendations. Evidence-Based Medicine Working Group. JAMA 1995; 274: 1800–1804.
19. Beck JR, Kassirer JP, Pauker SG. A convenient approximation of life expectancy (the "DEALE"). I. Validation of the method. Am J Med 1982; 73: 883–888.
20. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long-term survival and pattern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: Implications for a strategy of salvage transplantation. Ann Surg. 2002; 235: 373–382.
21. Cescon M, Cucchetti A, Grazi GL et al. Indication of the extent of hepatectomy for hepatocellular carcinoma on cirrhosis by a simple algorithm based on preoperative variables. Arch Surg 2009; 144: 57–63.
22. Park YK, Kim BW, Wang HJ, Kim MW. Hepatic resection for hepatocellular carcinoma meeting milan criteria in Child-Turcotte-Pugh class a patients with cirrhosis. Transplant Proc 2009; 41: 1691–1697.
23. D'Amico G, Garcia-Tsao G, Pagliaro L. Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. J Hepatol 2006; 44: 217–231.
24. Lü MD, Kuang M, Liang LJ et al. Surgical resection versus percutaneous thermal ablation for early-stage hepatocellular carcinoma: A randomized clinical trial. Zhonghua Yi Xue Za Zhi 2006; 86: 801–805.
25. Ueno S, Sakoda M, Kubo F et al., Kagoshima Liver Cancer Study Group. Surgical resection versus radiofrequency ablation for small hepatocellular carcinomas within the Milan criteria. J Hepatobiliary Pancreat Surg 2009; 16: 359–366.
26. Tanaka S, Noguchi N, Ochiai T et al. Outcomes and recurrence of initially resectable hepatocellular carcinoma meeting milan criteria: Rationale for partial hepatectomy as first strategy. J Am Coll Surg 2007; 204: 1–6.
27. Adam R, Azoulay D, Castaing D et al. Liver resection as a bridge to transplantation for hepatocellular carcinoma on cirrhosis: A reasonable strategy? Ann Surg 2003;238:508–518.
28. Del Gaudio M, Ercolani G, Ravaioli M et al. Liver transplantation for recurrent hepatocellular carcinoma on cirrhosis after liver resection: University of Bologna experience. Am J Transplant 2008; 8: 1177–1185.
29. Margarit C, Escartín A, Castells L, Vargas V, Allende E, Bilbao I. Resection for hepatocellular carcinoma is a good option in Child-Turcotte-Pugh class A patients with cirrhosis who are eligible for liver transplantation. Liver Transpl 2005; 11: 1242–1251.
30. Ikegami T, Shimada M, Imura S et al. The timing of liver transplantation after primary hepatectomy for hepatocellular carcinoma: A special reference to recurrence pattern and Milan criteria. Transplantation 2008; 86: 641–646.
31. Amin MG, Wolf MP, TenBrook JA Jr et al. Expanded criteria donor grafts for deceased donor liver transplantation under the MELD system: A decision analysis. Liver Transpl 2004; 10: 1468–1475.
32. Sarasin FP, Majno PE, Llovet JM, Bruix J, Mentha G, Hadengue A. Living donor liver transplantation for early hepatocellular carcinoma: A life-expectancy and cost-effectiveness perspective. Hepatology 2001; 33: 1073–1079.
33. Belghiti J, Cortes A, Abdalla EK et al. Resection prior to liver transplantation for hepatocellular carcinoma. Ann Surg 2003; 238: 885–892.
34. Cholongitas E, Marelli L, Shusang V et al. A systematic review of the performance of the model for end-stage liver disease (MELD) in the setting of liver transplantation. Liver Transpl 2006; 12: 1049–1061.
35. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: The BCLC staging classification. Semin Liver Dis 1999; 19: 329–338.
36. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: Chemoembolization improves survival. Hepatology 2003; 37: 429–442.
37. Cillo U, Vitale A, Grigoletto F et al. Prospective validation of the Barcelona Clinic Liver Cancer staging system. J Hepatol 2006; 44: 723–731.
38. Wang JH, Changchien CS, Hu TH et al. The efficacy of treatment schedules according to Barcelona Clinic Liver Cancer staging for hepatocellular carcinoma – Survival analysis of 3892 patients. Eur J Cancer 2008; 44: 1000–1006.
39. Bosch FX, Ribes J, Díaz M, Cléries R. Primary liver cancer: Worldwide incidence and trends. Gastroenterology. 2004; 127(S1): S5–S16.
40. Ravaioli M, Grazi GL, Ballardini G et al. Liver transplantation with the Meld system: A prospective study from a single European center. Am J Transplant 2006; 6: 1572–1577.

41. Piscaglia F, Camaggi V, Ravaioli M et al. A new priority policy for patients with hepatocellular carcinoma awaiting liver transplantation within the model for end-stage liver disease system. Liver Transpl 2007; 13: 857–866.
42. Vitale A, Saracino E, D'Amico FE et al. Prospective validation of a new priority allocation model for liver transplant candidates: An interim analysis. Transplant Proc 2009; 41: 1092–1095.
43. Yao FY, Ferrell L, Bass NM, Bacchetti P, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: Comparison of the proposed UCSF criteria with the Milan criteria and the Pittsburgh modified TNM criteria. Liver Transpl 2002; 8: 765–774.