

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

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Two treatments are accepted for patients with solitary hepatocellular carcinoma ≤ 5 cm in size and with preserved hepatic function: (1) liver resection, which can be performed without delay but has a high recurrence rate, and (2) liver transplantation, which has a better long-term survival, but is not easily available because grafts are scarce. A third possibility is to offer liver resection first and liver transplantation for tumor recurrence or deteriorating liver function ("salvage" transplantation). We investigated the implications of such a strategy with a Markov-based decision analytic model. In a scenario assuming intermediate values for 4 main variables (12-month waiting list; tumor progression outside transplantation criteria: 4% per month; recurrence after resection: 20% per year; recurrences eligible for transplantation: 60%), the life expectancy was 8.8 years for primary transplantation versus 7.8 years for primary resection and salvage transplantation, with a calculated use of grafts at 5 years of 52% for primary transplantation versus 23% for salvage transplantation. This study estimates of the survival and graft-saving of a strategy of primary resection and salvage transplantation according to variables that are to some extent predictable. This strategy may be a rational way to cope with lengthening waiting lists, especially for patients with tumors close to the limit for transplantation criteria, if the results of liver resection are good, if patients with the lowest risks of recurrence can be selected, and if a strict follow-up can detect recurrences when the patients are still transplantable. (HEPATOLOGY 2000;31:899-906.)

Hepatocellular carcinoma (HCC) is one of the most common tumors worldwide, and its incidence is increasing in

the western world because of the epidemics of the hepatitis C virus.¹

In patients aged less than 65 years, 2 therapies are currently accepted for early HCC (≤ 5 cm): partial hepatectomy (PH) and orthotopic liver transplantation (OLT).^{2,3} Although studies comparing the 2 treatments are retrospective and concern patients with disparate tumor characteristics and liver function,⁴⁻⁶ it is agreed that OLT is preferable to partial hepatectomy in patients with hepatic insufficiency and in patients with more than 1 tumor, in whom the results of liver resection are poor.

Patients with single tumors and preserved liver function present a therapeutic dilemma. Partial hepatectomy can cure the tumor immediately, with low mortality. The underlying cirrhosis, however, is responsible for a high recurrence rate, and the patient is exposed to the long-term complications of portal hypertension and hepatocellular failure.⁷ OLT, by treating both the tumor and the cirrhosis, offers a better long-term survival. The tumor, however, can outgrow the criteria accepted for transplantation while waiting for donor organs, affecting the ultimate outcome as shown in a previous analysis.²

For patients with a single resectable HCC, an alternative strategy to either partial hepatectomy or OLT would be to offer resection first and transplantation if the tumor recurs or if the liver function deteriorates (salvage OLT). Before such a strategy can be tested in a prospective controlled trial, the present study examines its implications in terms of patient outcome, graft use, and costs, using a decisional analysis model based on the data available in the literature.

PATIENTS AND METHODS

Decision Analytic Model

We investigated the impact of 2 options: (1) primary liver transplantation and (2) partial hepatectomy followed by salvage liver transplantation (Fig. 1A) in patients with compensated cirrhosis and solitary HCC ≤ 5 cm in diameter, with a Markov simulation (Decision Maker 7.1, Pratt Medical Group, Boston, MA). The use of this model is now well established in the study of chronic disease.⁸⁻¹⁰ The model followed hypothetical patients over time as they moved among different states of health and determined the likely outcomes. Each state of health was defined by clinical descriptors (written in small capitals therein, and summarized in Fig. 1B). The likelihood and timing of adverse and beneficial events determined the outcome. All patients began the simulation with a diagnosis of COMPENSATED CIRRHOSIS AND SINGLE HCC ≤ 5 cm in diameter. In the PARTIAL HEPATECTOMY option (Fig. 1B), patients underwent liver

Abbreviations: HCC, hepatocellular carcinoma; PH, partial hepatectomy; OLT, orthotopic liver transplantation.

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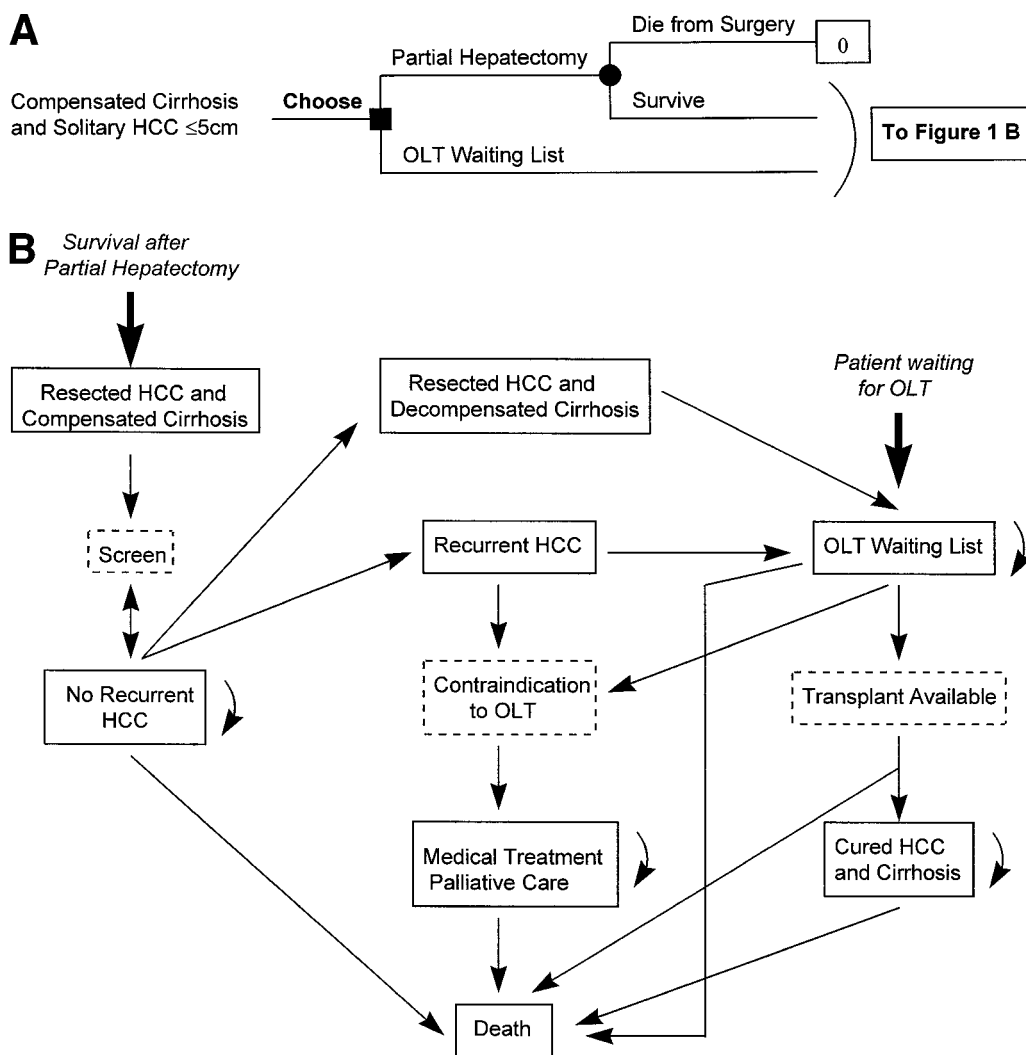


FIG. 1. (A) Decision tree. This panel represents the choice between the 2 strategies, primary liver transplantation (primary OLT), and partial hepatectomy and salvage liver transplantation (salvage OLT). (B) States of health in the decision model. Each *square* represents a state of health. *Straight arrows* represent the changes that may occur during each month. *Circular arrows* signify that the patient remains in the same state of health.

resection and went on to the RESECTED HCC AND COMPENSATED CIRRHOSIS STATE, where US screening was performed every 3 months to detect recurrent tumor (SCREEN). After each screening, whereas some patients remained in the same state of health, others developed complications, such as decompensated cirrhosis (RESECTED HCC AND DECOMPENSATED CIRRHOSIS), tumor recurrence (RECURRENT HCC), or death resulting from age-, gender-, and compensated cirrhosis-related specific mortality rates. Patients with recurrence could have a tumor outside the criteria accepted for transplantation (>5 cm for single tumors or >3 cm for multiple tumors, or >3 tumors, vascular or extrahepatic spread),¹¹ and received supportive therapy only (MEDICAL TREATMENT, PALLIATIVE CARE). In the palliative care state, survival was determined by the incurable cancer-related specific mortality in addition to the mortality from the underlying cirrhosis. Patients diagnosed with a curable recurrent tumor (RECURRENT HCC) and those presenting with features of decompensated cirrhosis (RESECTED HCC AND DECOMPENSATED CIRRHOSIS) were considered suitable candidates for liver transplantation. Thus, an organ donor and subsequent transplantation could be available during any of the simulated months (OLT WAITING LIST). While waiting for organ donors, all patients faced the risk of dying from cirrhosis-related complications. Patients with recurrent HCC also faced the risk of developing tumor-related complications, such as tumor growth and spread, contraindicating OLT (CONTRAINDICATION TO OLT). If OLT was performed, and if patients survived the procedure, they moved to the CURED HCC AND CIRRHOSIS state, which determined long-term prognosis according to survival data following OLT-for-HCC. Patients having the option of receiving a transplant as a first-line

therapy (Fig. 1A) faced the risks of dying or developing contraindications to transplantation while waiting for it. If an organ was available and if they survived the procedure, their prognosis was dependent on OLT-for-HCC survival data.

Assumptions

In constructing our model we made several assumptions based on data available in the literature or on accepted or justifiable clinical attitudes.

1. In our analysis, we considered only patients less than 60 years of age without associated diseases susceptible to limit life expectancy in addition to underlying compensated cirrhosis (Child-Pugh class A) and with a solitary tumor within the criteria commonly accepted for transplantation (HCC not exceeding 5 cm in diameter, no tumoral invasion of the portal or hepatic veins, and no extrahepatic spread of the tumor).

2. Following partial hepatectomy, patients could develop clinical features of decompensated cirrhosis (Child B/C). Because of the lack of data on the incidence of decompensation after liver resection, we assumed the rate of patients presenting clinical features of Child B/C cirrhosis to be at best similar to that of patients without HCC.

3. Following partial hepatectomy, we considered that progression to Child B/C class was an indication for OLT, even in the absence of HCC recurrence.

4. We defined HCC recurrence as a new tumor detected on high-resolution ultrasound, and we assumed that all patients with presumed recurrent HCC detected on ultrasound underwent preoperative investigations including computed tomography and/or mag-

netic resonance imaging to determine: (1) whether ultrasound was a false-positive result and (2) whether patients were suitable candidates for OLT.

5. We assumed that small HCC (≤ 5 cm) without vascular involvement or extrahepatic spread carried no additional specific mortality in addition to that of the underlying cirrhosis.

6. The shortage of organ donors meant that HCC patients faced the risk of the tumor spreading while waiting for OLT. We assumed that, in a population where the size of the tumors is distributed evenly, patients with the largest tumors started crossing the 5-cm threshold for transplantation early during the waiting time and that the fraction of small HCC outgrowing the criteria for OLT was constant over time.

7. We considered the criteria for secondary OLT for recurrent HCC to be the same as the criteria for primary OLT.

8. After partial hepatic resection, the proportion of patients with recurrent HCC who still fulfill the criteria for OLT is unknown. This proportion depends on the quality of a surveillance program, on the compliance of the patients, and on the patient's age and associated illnesses. We assumed that the proportion of patients transplantable at the time of HCC recurrence (transplantability) could vary between 40% and 80%.

9. For patients undergoing OLT because of recurrent HCC, we assumed the perioperative mortality to be identical to primary OLT and the 5 year survival to be 10% less than primary OLT, as some recurrent tumors may be intrahepatic metastases from the original tumor and may have an increased tendency for distant spread.

Data Sources

Probabilities were drawn from examination of all articles identified in a MEDLINE search. Table 1 summarizes the baseline probabilities and rates used in the model (baseline analysis). Also, because published studies vary in their estimates of the variables used in our baseline analysis, we studied the effect of varying each parameter over a range to determine whether the outcome of the strategies changed (sensitivity analysis). The ranges of such variations are given in Table 1.

Summary of the Data Used for Baseline and Sensitivity Analysis

Cirrhosis: Natural History and Prognosis. Long-term studies indicate that 5-year survival rates range from 65% to 85%, and that once decompensation has occurred, 5-year survival ranges from 20% to 40%.¹²⁻¹⁵ Between 5% and 10% of patients with compensated cirrhosis develop features of decompensation each year.^{14,15}

Waiting-List Time for OLT. The waiting-list time for liver transplantation varies according to the blood group and the local organ donation rate, with a median of 477 days in 1997 in the United States.¹⁶ We considered that the waiting time varied between 6 and 18 months.

Proportion of Patients With HCC Developing Contraindications to OLT While Waiting for Transplantation. The rate of tumor progression outside the criteria for transplantation while on the waiting list has been reported recently.¹⁷ In a population with a mean tumor size of 24 ± 13.8 mm, 6 of 37 patients dropped out because of tumor progression in a list with a mean waiting time of 162 days (3.0% per month). We assumed that the initial drop-out rate in our population, with tumors as large as 5 cm, would be higher and took a baseline drop-out rate of 4%, with values for sensitivity analysis of 3% and 5%. These assumptions are in keeping with studies reporting that one-third of small HCC grows rapidly (doubling time 60 days), implying that a tumor of 3 cm would require 3 to 4 months to exceed 5 cm in diameter,¹⁸⁻¹⁹ and with previous work estimating that 30% of small HCCs would outgrow OLT criteria within each 6-month time interval (5% per month).²

OLT-Related Long-Term Prognosis. For patients transplanted with single HCC ≤ 5 cm, no vascular invasion, and no extrahepatic spread, we considered a 5-year survival rate of 70%.^{6,11,20} For patients with recurrent HCC ≤ 3 nodules ≤ 3 cm or a single nodule

TABLE 1. Rates* and Probabilities† Extracted From Literature and Used in the Analysis

Variable (Reference)	Baseline Analysis	Literature Range Tested
Compensated cirrhosis-related prognosis		
5-year survival	75%	65%-85%
Annual mortality rate‡ ¹²⁻¹⁵	0.05	0.08-0.03
Decompensated cirrhosis-related prognosis		
5-year survival	30%	20%-40%
Annual mortality rate ¹²⁻¹⁵	0.23	0.31-0.17
Compensated to decompensated cirrhosis annual transition probability ^{14,15}	7.5%	5%-12%
OLT-related prognosis (<i>patients with curable recurrent HCC and compensated cirrhosis</i>)		
5-year survival	60%	50%-70%
Annual mortality rate ^{6,11,20}	0.1	0.13-0.07
OLT-related prognosis (<i>patients with decompensated cirrhosis</i>)		
5-year survival	70%	60%-80%
Annual mortality rate ^{11,20,21}	0.07	0.1-0.04
OLT-related 3-month mortality (<i>patients with curable recurrent HCC and compensated cirrhosis</i>) ^{3,11,21,22}	8%	5%-10%
OLT-related 3-month mortality (<i>patients with decompensated cirrhosis</i>) ^{3,11,21,22}	8%	5%-10%
Partial hepatectomy-related 3-month mortality ^{3,22-24}	5%	3%-7%
Incurable HCC-related prognosis		
3-year survival	28%	10%-30%
Annual mortality rate ²⁹⁻³¹	0.42	2.2-0.9
HCC recurrence rate (per year)		
After partial hepatectomy ^{7,23,25-28}	20%	10%-30%
Fraction of HCC patients developing OLT contraindications while waiting for organ donors (per month) ^{2,17-19}	4%	3%-5%

*Using the assumption of a declining exponential approximation to survival, the annual excess mortality can be expressed as the reciprocal of life expectancy, which itself can be calculated as $-(\ln S)/t$, where t is time at which survival S is measured.

†Transition probabilities were calculated for the Markov simulation from annual rates using the formula: probability = $\exp(-\text{annual rate} \times \text{cycle length})$.

‡In addition to the mortality related to the patient's specific age and gender.

≤ 5 cm, we considered a survival rate of 60% (sensitivity analysis 50% to 70%).

OLT-Related 3-Month Mortality. We considered the 3-month mortality of OLT to be 8%, according to the data published in recent series of OLT for HCC that range from 3% to 10%.^{3,11,21,22}

Partial Hepatectomy-Related 3-Month Mortality. We considered the 3-month mortality of partial hepatectomy to be 5%, ranging between 3% and 8%, considering that all patients had compensated cirrhosis.^{3,17,22-24}

HCC Recurrence Rate After Partial Hepatectomy. The rate of recurrence of HCC after partial hepatectomy varies according to the different series and to the characteristics of the patients in each series. We considered the rate of recurrence of HCC after partial hepatectomy for single tumors ≤ 5 cm to vary between 15% per year to 25% per year.^{7,17,23,25-28}

For the sake of clarity in the decisional analysis model, we created 3 scenarios in which both the recurrence rate and the transplantability rate varied in a sense either both favoring the strategy of resection and salvage transplantation, or both penalizing it. In the *best case scenario*, we hypothesized a yearly recurrence rate after resection of 15%, and transplantability after recurrence of 80%. In the *intermediate case scenario*, we hypothesized a yearly recurrence rate of 20% after resection, and a transplantability after recurrence of 60%. In the *worst case scenario* we hypothesized a 25% recurrence rate and a transplantability of 40%.

TABLE 2. Average Direct Costs (US\$) for Preoperative Investigations, Treatment Procedures, and Outcomes

Item	Baseline Costs	Ranges Used in Sensitivity Analyses
Preoperative investigations		
Computed tomography	800	500-1,200
Magnetic resonance imaging	1,200	1,000-1,400
Arteriography	1,300	1,000-1,500
Others*	8,000	6,000-10,000
Follow-up while waiting for OLT†		
Compensated liver disease	1,000	800-1,200
Decompensated liver disease	3,800	3,000-5,000
Surgical treatment‡		
Partial hepatectomy	35,000	30,000-40,000
OLT	150,000	100,000-200,000
US screening	300	200-400
Outcomes (yearly ambulatory care)		
After hepatectomy	3,000	2,000-4,000
After OLT	12,000	10,000-14,000
Follow-up if contraindication to OLT (yearly palliative care)	35,000	30,000-40,000

*Includes costs for (1) routine preoperative laboratory procedures (e.g., chemistry); (2) chest radiograph and ECG; (3) pulmonary function tests; and (4) daily room costs on medical ward multiplied by the estimated duration of stay (5 days).

†Monthly costs including medical evaluation with physical examination, laboratory procedures, treatment of complications (e.g., variceal hemorrhage, refractory ascites), and ultrasonography once a month.

‡Includes intervention-related costs, intensive care unit-related costs, and daily room costs on surgical ward, multiplied by the estimated duration of stay in each unit (4 days and 10 days, respectively), additional costs for ancillary tests/routine laboratories procedures and radiograph), and intensive care unit-related daily costs multiplied by the estimated duration of stay before eventual death resulting from complications within 30 days.

Incurable HCC-Related Prognosis. For patients presenting contraindications to OLT after tumor recurrence and receiving medical palliative therapy, we considered a survival of 28% at 3 years,²⁹ ranging from 15% to 35% at 3 years.^{30,31}

Patient's Age- and Gender-specific Mortality Rate. The mortality related to patient's age, gender, and race was calculated from standard tables of vital statistics by taking the reciprocal of the life expectancy.³² Survival data were used to calculate cirrhosis- and cancer-

specific excess mortality rates using the exponential approximation of life expectancy (DEALE).³³

Cost Analysis

Our analysis included all direct health-related costs (in 1998 U.S. dollars) associated with each strategy, assessed from a societal perspective and discounted at 3% per year.³⁴ Indirect costs, such as lost earnings caused by poor health, were not estimated. Table 2 summarizes our hospital's average variable costs for each intervention modeled. These costs are comparable with those of U.S. institutions.³⁵⁻³⁷ Variable costs assume that institutional superstructure is already in place (e.g., laboratories). To calculate a cost-benefit ratio, we considered the less effective strategy to be the reference strategy, so that a cost per additional year gained with the alternative strategy could be calculated. We did not include in the analysis the financial and social cost of a graft (beside the costs of liver transplantation), because neither the data nor the biometric and economical tools are available for such analysis at present.

RESULTS

Life Expectancy and Graft Use

The life expectancy for each strategy varied according to: (1) the waiting time for OLT; (2) the drop-out rate on the waiting list; (3) the yearly recurrence rate of HCC after resection; and (4) the transplantability of patients with recurrent HCC. Recurrence and transplantability rates were grouped into a best-, intermediate-, and worst-case scenario either favoring or penalizing the strategy of primary resection and salvage transplantation, as described earlier. Assuming baseline values for all 4 main variables (waiting time 12 months, drop-out rate 4%, and intermediate case scenario: tumor recurrence rate 20% and transplantability 60%), the average life expectancy for a 55-year-old male with a single HCC and preserved liver function was 8.8 years for primary OLT and 7.6 years for PH-salvage OLT. In this scenario, the number of grafts used after 5 years (of a theoretical number of 100 grafts if all patients were submitted to transplantation immediately) was 52% for primary OLT and 23% for PH-salvage OLT. Table 3 summarizes the results of the baseline analysis, and the results according to changes in the 4

TABLE 3. Mean Life Expectancy (Years) for Primary Liver Transplantation and for Primary Resection and Salvage Liver Transplantation, According to the Waiting-List Time, the Monthly Drop-out Rate, the Yearly Tumor Recurrence Rate, and the Proportion of Patients With Recurrence Who Fulfill the Criteria for Transplantation (Transplantability)

Waiting-List Time	Monthly Drop-out Rate	Primary OLT	Primary Partial Hepatectomy and Salvage OLT		
			Scenarios		
			Best Case Yearly Recurrence 15% Transplantability 80%	Intermediate Case Yearly Recurrence 20% Transplantability 60%	Worst Case Yearly Recurrence 25% Transplantability 40%
6 months	3%	12.2	10.0	8.9	7.8
12 months		10.1	9.0	8.0	7.1
18 months		8.1	8.1	7.3	6.4
6 months	4%	11.5	9.7	8.6	7.5
12 months		8.8	8.4	7.6	6.7
18 months		6.0	7.1	6.4	5.8
6 months	5%	10.8	9.3	8.4	7.3
12 months		7.4	7.7	7.0	6.2
18 months		4.0	6.1	5.6	5.1

NOTE. The calculations assume a 70% 5-year survival for primary OLT and a 60% 5-year survival for salvage OLT for recurrence, as some recurrent tumors may be metastases from the original tumor and may carry a worse outcome. The shaded figures correspond to the intermediate value for all of the variables considered.

variables mentioned earlier (multiple way sensitivity analysis). At the extreme most favorable to primary liver transplantation: monthly drop-out rate 3%, waiting time 6 months, and worst case scenario (recurrence rate 25%, transplantability 40%), the difference in mean life expectancy between primary OLT and PH-salvage OLT was 4.4 years (12.2 vs. 7.8 years). The number of grafts used at 5 years in these circumstances was 82% for primary OLT versus 29% for PH-salvage OLT. In a scenario more favorable to PH-salvage transplantation: drop-out rate 5%, waiting time 12 months, and best case scenario (recurrence rate 15% and transplantability 80%), the difference between primary OLT and PH-salvage OLT was 2.1 years in favor of salvage OLT (4 years vs. 6.1 years), with a use of liver grafts at 5 years of 40% for primary OLT versus 18% for PH-salvage OLT. Figure 2 shows the changes in the average life expectancy and in the use of grafts according to a sensitivity analysis with a fixed drop-out rate of 4% per month.

The calculated survival curve for primary OLT and for PH-salvage OLT in the best, intermediate, and worst scenarios with a fixed waiting time of 12 months and a drop-out rate of 4% per month, are represented in Fig. 3. The corresponding curves for graft use are represented in Fig. 4.

Sensitivity Analysis for the Remaining Variables

We performed additional sensitivity analyses on all other variables in the model. Increasing the 5-year survival of transplantation for recurrent HCC to 70% resulted, in the baseline scenario, in a life expectancy of 8.2 years for PH-salvage OLT (as compared with 8.7 years for primary OLT). Decreasing the 5-year survival of transplantation for recurrent HCC to 50% resulted, in the baseline scenario, in a life expectancy for PH-salvage OLT of 6.6 years. The graft use at 5 years did not change with this sensitivity analysis, with 23% for PH-salvage OLT, as compared with 52% for primary OLT. Sensitivity analysis for other variables did not change significantly the results summarized earlier.

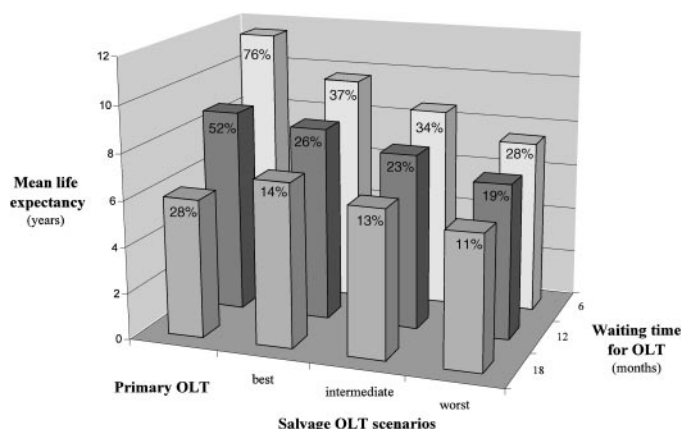


FIG. 2. Calculated mean life expectancy after primary OLT and after salvage OLT (best case scenario: yearly recurrence rate after resection 15% and transplantability of recurrences 80% of the patients with recurrence qualifying for liver transplantation; intermediate-case scenario: recurrence 20% and transplantability 60%, and worst-case scenario: recurrence 25% and transplantability 40%). The influence of the time on the waiting list is represented on a horizontal axis, assuming a monthly drop-out rate of 4% because of tumor progression. Five-year survival rates of 70% after primary transplantation and of 60% after salvage transplantation are assumed. Figures on the bars represent the percentage of liver grafts used at 5 years in each strategy and scenario.

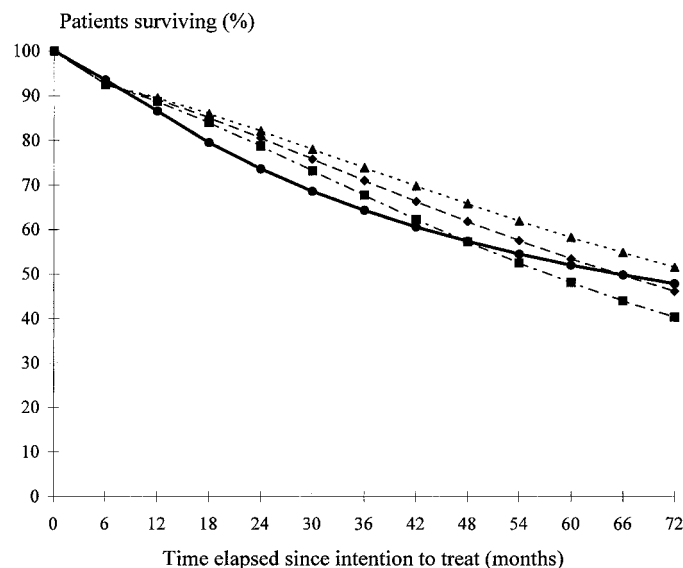


FIG. 3. Calculated survival curves for primary OLT and salvage OLT, assuming a waiting list of 12 months and a monthly drop-out rate of 4%. In the salvage OLT strategy the best case scenario corresponds to a tumor recurrence rate after resection of 15% per year and a transplantability of 80%; the intermediate-case scenario corresponds to a recurrence rate of 20% per year and a transplantability 60%; and the worst-case scenario corresponds to a recurrence rate of 25% per year and a transplantability of 40%. Five-year survival rates of 70% after primary transplantation and of 60% after salvage transplantation are assumed. Primary OLT (●). Salvage OLT scenarios: best (▲), intermediate (◆), worst (■).

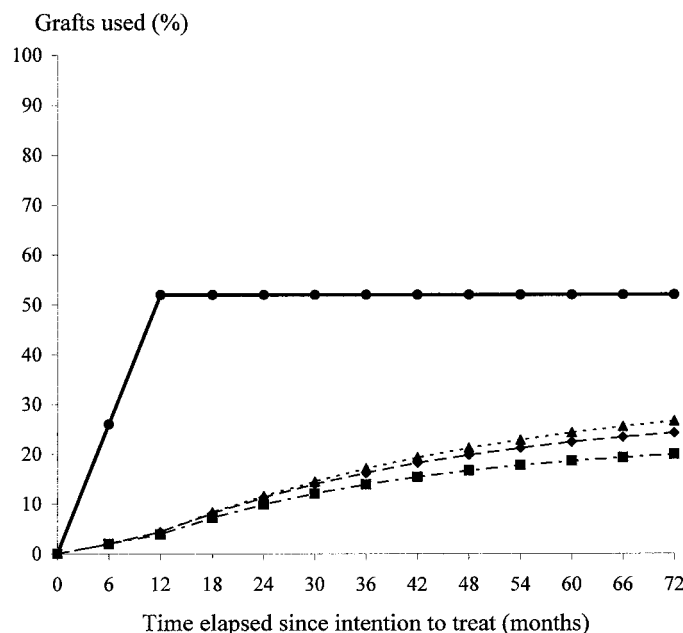


FIG. 4. Calculated graft use for primary OLT and salvage OLT, assuming a waiting list of 12 months and a monthly drop-out rate of 4%. In the salvage OLT strategy, the best-case scenario corresponds to a tumor recurrence rate after resection of 15% per year and a transplantability of 80%; the intermediate-case scenario corresponds to a recurrence rate of 20% per year and a transplantability 60%; and the worst-case scenario corresponds to a recurrence rate of 25% per year and a transplantability of 40%. Primary OLT (●). Salvage OLT scenarios: best (▲), intermediate (◆), worst (■).

Cost Analysis

Cost analysis for both strategies showed that primary resection and salvage transplantation was less expensive in all scenarios considered, with discounted lifetime costs in the baseline scenario of \$255,557 for OLT and \$206,920 for PH-salvage OLT. In the baseline scenario, the cost per additional year gained with primary OLT, as opposed to PH-salvage OLT, (cost/effectiveness ratio) was \$27,932. For a waiting time of 6 months, the cost/effectiveness ratio was \$25,716, and for a waiting time of 18 months, the cost/effectiveness ratio became negative, as the strategy of PH-salvage OLT was at the same time more effective and less expensive. For a best-case scenario, maintaining the drop-out rate at 4%, the cost/effectiveness ratio was \$31,086 for a waiting time of 6 months and \$71,564 for a waiting time of 12 months. For a worse-case scenario, the cost-effectiveness/ratio ranged from \$25,530 for a waiting time of 6 months to \$92,422 for a waiting time of 18 months. Additional sensitivity analyses of costs of procedures did not alter notably the results detailed earlier.

DISCUSSION

Although the strategy of primary resection of HCC and salvage OLT for recurrence or for worsening liver function has never been formally evaluated, it is used in several transplantation units (including ours) under the pressure of organ shortage. The consequences of such a strategy, however, are difficult to assess because several parameters have to be considered simultaneously. This study compares primary resection and salvage transplantation versus primary liver transplantation, using a biometrics model based on available data, that predicts survival and resource use for complex clinical scenarios.

The model showed that the main 4 variables determining the outcome of primary resection and salvage transplantation were the duration of the waiting list before OLT, the rate at which the tumor out-grew the criteria for transplantation, the tumor recurrence rate after resection, and the transplantability at the time of recurrence. Assuming for these variables values in the middle of the range defined in this study (intermediate case scenario), the average life expectancy provided by the strategy of primary resection and salvage OLT was 7.6 years, as compared with 8.8 years for primary OLT. This difference was associated to an estimated saving of 29% of liver grafts at 5 years. A life expectancy similar in the 2 strategies (8.4 years for PH-salvage OLT) was obtained if a recurrence rate after resection of 15%, and a transplantability rate of 80% (best case scenario) can be assured, this despite assuming that the 5-year survival after salvage OLT was 10% lower than after primary OLT. In this scenario, the number of grafts used after 5 years was 52% for primary OLT and 26% for PH-salvage OLT, representing a saving of 26% of donor organs. This saving can be explained by 2 factors.

First, in primary OLT, grafts would be used for the 30% of patients who die in the 5-year interval, whereas no grafts would be used for patients dying postoperatively after the resection (5%), or for patients who would not qualify for transplantation at the time of recurrence (20%).

Second, with a recurrence rate constant at 15% per year, HCC would not recur after resection in a considerable number of patients (44% at 5 years). These patients would

receive an unnecessary graft in primary OLT. Although such a low recurrence rate is difficult to obtain in the general population of HCC patients submitted to resection, it can be achieved in selected groups, such as patients with low inflammatory activity³⁸ and low transaminase values³⁹ or with the advent of medications that lower the recurrence rate, as shown in a pilot study using retinoids.⁴⁰

Cost analysis in our model showed that the cost per additional year offered by the strategy of primary transplantation varied between \$25,530 and \$92,422 according to the different scenarios. As the strategy of primary PH-Salvage OLT was uniformly less expensive than primary OLT, the cost-efficiency ratio became negative (and therefore meaningless) for scenarios in which primary PH-salvage OLT had a survival advantage over primary OLT. Ideally, the cost analysis of our model should have included analysis of quality of life (QALY). Data on the quality of life after resection and after transplantation for HCC are limited, however, and our conclusions would have been speculative. Also, we did not include in the analysis the economical and social costs of grafts, that are consumed differently in the 2 strategies. The value of grafts can vary according to the potential for their use, to the composition and length of a waiting list, and to the balance between supply and demand. The biometric tools for such analysis are still untested and should be the object of a separate study.

The survival figures of OLT for HCC in our model are lower than the figures reported commonly in the literature. In fact our model assumes an intention to treat and integrates the mortality of the patients dropping-out from the waiting list. Survival figures similar to the ones calculated by our model were reported recently in a prospective study of OLT for HCC,¹⁷ showing the considerable impact of the waiting time and the rate of tumor growth on the waiting list on the ultimate results of OLT for HCC. This has been suggested in a previous study from our unit.²

Our study focused on patients with single small tumors and compensated cirrhosis because in these patients both liver resection and OLT are accepted as primary treatments. Given the high recurrence rate of HCC after partial hepatectomy, however, treatment by liver resection alone, without the possibility of rescue by transplantation, gives a suboptimal survival benefit, and we did not consider it as a realistic possibility in our analysis.

We considered partial hepatectomy as the preferred method for ablation of HCC because it is not universally accepted that alternative treatments offer the same radicality. In expert hands, however, percutaneous ethanol injection achieves local recurrence rates as low as 5% to 8%, with lower cost, morbidity and mortality as compared with resection,⁴¹⁻⁴³ at least for tumors smaller than 4 cm.²³ Other authors have reported similarly good results with radio-frequency thermal tumor ablation.⁴⁴ If such techniques can achieve results equal to resection in the local control of the tumor (and therefore in the recurrence rate), applying them to our model would probably not change the results of our analysis. In fact, percutaneous techniques of tumor destruction may be better than surgery in terms of early mortality and preservation of liver function, 2 factors favoring a strategy of salvage transplantation.

The main limitation of our analysis is that reliable data are lacking on some parameters such as the rate of deterioration of liver function after partial hepatectomy, or the rate of

transplantability of recurrences. Where evidence was insufficient, however, we deliberately chose figures penalizing the strategy of primary resection and salvage liver transplantation that we wanted to test. Accordingly, we attributed to salvage transplantation a 5 year survival of 60%, assuming that in some cases recurrence after resection may be intrahepatic metastases,⁴⁵ and that these tumors may have increased potential for distant spread. In a recent report, however, recurrent disease developed in only 1 of 12 patients transplanted for recurrent HCC after resection,⁴⁶ and it is possible that the survival figures will need adjusting in favor of salvage transplantation. Other factors in addition to the ones we considered might affect the outcome, and decision analysis should not replace prospective trials.

With the present study, we do not imply that the strategy of primary resection and salvage OLT is to be preferred to primary OLT, nor feel apt to encourage its application. The analysis offers a tool to understand the implications of such a strategy, given variables that it is possible to know in each center (such as the waiting list time, or the applicability of a tight follow-up program), or that are to some extent predictable in an individual patient (such as the risk of tumor progression outside the criteria for larger tumors or the rate of recurrence after resection). At one extreme, if the recurrence rate after resection is too high, primary partial hepatectomy and salvage OLT is of no advantage as compared with primary OLT (at best it procrastinates transplantation), if the transplantability at the time of recurrence is low (it penalizes patients who undergo resection first), and if grafts are readily available. In the current situation of donor shortage, however, primary resection and salvage OLT may be a rational way to cope with lengthening waiting lists, especially for patients close to the drop-out threshold or for patients with the lowest risk of recurrence after partial hepatectomy, provided that the results of liver resection are good and that high standards in the follow-up of patients can be achieved.

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