LIVER AND BILIARY DISEASE

Cost effectiveness of adjuvant therapy for hepatocellular carcinoma during the waiting list for liver transplantation

J M Llovet, X Mas, J J Aponte, J Fuster, M Navasa, E Christensen, J Rodés, J Bruix

Gut 2002;**50**:123–128

See end of article for authors' affiliations

Correspondence to: Dr J M Llovet, BCLC Group, Liver Unit, IDIBAPS, Hospital Clínic, c/Villarroel 170, 08036-Barcelona, Catalonia, Spain; jmllovet@clinic.ub.es

Accepted for publication 29 March 2001

Background: Survival after liver transplantation for early hepatocellular carcinoma (HCC) is worsened by the increasing dropout rate while waiting for a donor.
Aims: To assess the cost effectiveness of adjuvant therapy while waiting for liver transplantation in HCC patients.
Method: Using a Markov model, a hypothetical cohort of cirrhotic patients with early HCC was considered for: (1) adjuvant treatment—resection was limited to Child-Pugh's A patients with single tumours, and percutaneous treatment was considered for Child-Pugh's A and B patients with single tumours unsuitable for resection or with up to three nodules < 3 cm; and (2) standard management. Length of waiting time ranged from six to 24 months.
Results: Surgical resection increased the transplantation rate (>10%) and provided gains in life expectancy of 4.8–6.1 months with an acceptable cost ($40 000/ year of life gained) for waiting lists ⩾1 year whereas it was not cost effective ($74 000/life of year gained) for shorter waiting times or high dropout rate scenarios. Percutaneous treatment increased life expectancy by 5.2–6.7 months with a marginal cost of approximately $20 000/year of life gained in all cases, remaining cost effective for all waiting times.
Conclusions: Adjuvant therapies for HCC while waiting for liver transplantation provide moderate gains in life expectancy and are cost effective for waiting lists of one year or more. For shorter waiting times, only percutaneous treatment confers a relevant survival advantage.

Surgical resection and orthotopic liver transplantation (OLT) are considered the first treatment options for hepatocellular carcinoma (HCC) although the best treatment strategy has not been established.[1] Resection achieves good results in only a minority of patients but the long term outcome is worsened by a high recurrence rate (three year recurrence rate of 50%).[2–5] In contrast, liver transplantation offers excellent results (70% survival with less than 20% recurrence at five years) if the indication is restricted to patients with single tumours ⩽5 cm or three nodules <3 cm.[4 6–8] These values have prompted most hepatologists to favour OLT as firstline treatment. However, the shortage of donors and the increasing demand of organs have lengthened waiting times to more than six or 12 months in Europe and USA, respectively.[9 10] This delay can allow the tumour to grow to stages that contraindicate OLT. We have recently shown that a waiting time longer than six months is associated with a 23% rate of dropout from the waiting list,[4] and values of up to 30–40% have been reported both in Europe and USA,[9 11] which may reach 50% when expanded selection criteria are applied.[12] This sharply worsens the outcome when assessing OLT results on an intention to treat basis.

Several adjuvant antitumoral therapies have been administered to patients on the waiting list for liver transplantation to reduce tumour growth. The most common treatment is chemoembolisation, a palliative option that may achieve extensive tumour necrosis.[13–18] However, there are no prospective studies showing that it is effective in reducing the dropout rate or in modifying the outcome of these patients. Surprisingly, the usefulness of more radical options, such as resection or percutaneous ablation, that may provide the majority of patients with complete tumoral responses, are seldom used as adjuvant treatments prior to OLT. Randomised controlled trials (RCTs) assessing the benefits of any of these therapeutic approaches are unlikely to be performed because they would be costly and require a very large sample size. Therefore, we designed a decision analysis to assess the impact of treating HCC patients on the waiting list for OLT with the probability of being transplanted, overall survival, and cost effectiveness. Adjuvant therapies included surgical resection and percutaneous ablation as they provide a more extensive tumour load reduction than chemoembolisation. The model takes into account the heterogeneity of HCC candidates according to their tumour stage/liver functional impairment and the variable duration of the waiting times throughout the world. This stratification allows the reader to identify into which scenario their patient fits and thus use the obtained outputs for rational clinical decision making and also to correctly allocate health care resources in the management of this complex disease.

PATIENTS AND METHODS

Design of the study and Markov multistate transition model

We analysed the cost effectiveness of applying resection or percutaneous ethanol injection (PEI) versus standard management in cirrhotic patients with early HCC on their inclusion on the waiting list for OLT. A Markov multistate transition model was developed to estimate the impact of treatment on the probability of being transplanted, overall outcome, and cost effectiveness. A commercially available software product (Data 3.5;Tree Age Software, 1998, Williamstown, Massachusetts, USA) was used to generate the model and to tabulate all costs accrued in each group. The study was performed according to the recommendations of the Panel of

Abbreviations: CEA, cost effectiveness analysis; HCC, hepatocellular carcinoma; OLT, orthotopic liver transplantation; RCT, randomised controlled trial; PEI, percutaneous ethanol injection; RF, radiofrequency; LE, life expectancy; MCYLS, marginal cost per year of life saved.

Cost-effectiveness in Health and Medicine of the US, and following their indications in reporting cost effectiveness analysis (CEA).[19 20]

Target population and adjuvant treatments

The study focused on HCC candidates for OLT as the primary treatment option. This target population included patients with early HCC (single tumour ⩽5 cm or three nodules ⩽3 cm) on an otherwise non-advanced liver cirrhosis (Child-Pugh's A and B classes) without associated diseases. We did not consider Child-Pugh's C class cirrhotic patients with coincidental tumours because their dropout rate is mostly related to life threatening decompensation of cirrhosis rather than tumour progression.

Our model considered two reference cases of HCC candidates for OLT which were stratified according to tumour stage and liver function impairment.

Reference case No 1 (group 1). Child-Pugh's A patient with a single HCC ⩽5 cm, treated by surgical resection. This treatment provides an acceptable morbidity and short term mortality.[2–5]

Reference case No 2 (group 2). Patients with either a single HCC ⩽5 cm and Child-Pugh's B or with three tumours ⩽3 cm. As these patients are poor candidates for resection due to their high risk of postoperative decompensation with associated death, they were considered for PEI.

PEI is a highly effective option that provides complete necrosis in 70–80% of cases in tumours smaller than 3 cm.[21–24] This treatment has been widely assessed throughout the world over the last decade, with a safety profile and a low risk of tumour seeding along the needle tract (0.6% cases per patient; 0.08% per session).[25] Percutaneous radiofrequency (RF) ablation was not considered in the model because reliable data on antitumoral usefulness and cost have not been completely established. In addition, we have recently reported a noteworthy rate of needle track seeding related to this procedure, thus increasing the concerns regarding its application prior to OLT.[26] Chemoembolisation was also not considered because of its lower antineoplastic effect if compared with surgery or percutaneous ablation, and because of the lack of prospective data showing a beneficial effect. Patients in the control arm were considered to receive no specific antineoplastic treatment, which represents the standard management of patients on the waiting list of our transplantation programme to date.[4 7]

Decision tree and states of health

A diagram of the event pathway is depicted in fig 1. Analysis of the state of health was performed in three month cycles starting from inclusion of patients onto the waiting list until a time period of 10 years after OLT. In summary, patients with early HCC were allocated to receive adjuvant treatment according to their risk group or standard management on inclusion onto the waiting list. Patients of reference case No 1 underwent resection and entered the waiting list state. Three transition states were considered thereafter: (a) receiving OLT and entering the post-transplantation state; (b) developing any contraindication for OLT and entering the dropout state; or (c) dying of tumour progression or complications of cirrhosis. Similarly, patients of reference case No 2 received PEI treatment and entered the waiting list state where the same three transition states were considered. Finally, patients in the non-treatment arm directly entered the waiting list state without antitumoral treatment where the three transitional states were again considered. Patients effectively transplanted entered the post-transplantation state until death.

Summary of data and assumptions

Survival and recurrence on the waiting list

Data and assumptions used in the decision analysis for the reference cases are depicted in table 1. In Child-Pugh's A patients with a single HCC, the probability of survival after resection was considered to be 93% and 75% at one and two years, respectively. Recurrence rate at two years was 30%.[3–5] Complete response after PEI was related to tumour size, and ranged from 80% for single tumours <3 cm, 50% for tumours of 3–5 cm, to 40% for patients with up to three nodules smaller than 3 cm.[21–24] Survival outcome after PEI varied according to achievement of a complete and maintained response, and ranged from 62% to 72% at two years. The two year recurrence rate—new tumour development—was considered to be 25%.[21–24]

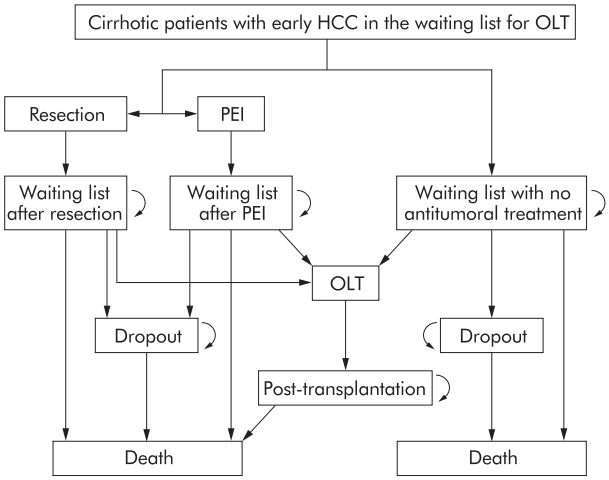

Figure 1 Diagram of the event pathway: decision tree and states of health.

Survival data for the non-treatment arm were derived from prospective studies on the prognosis of patients diagnosed with asymptomatic HCC without vascular invasion or extrahepatic spread: one and two year survival rates of 80% and 65%, respectively.[27] Mortality of these patients is due to HCC itself, and eventually to complications of cirrhosis. Age related mortality in the periods of time considered was negligible.

Dropout rate

Data on dropout rate of HCC candidates for OLT are rarely reported. We reported a 23% dropout rate on a six month median waiting list[4] whereas other authors have described even higher incidences of 30–40% while waiting for more than one year.[9 11] In our model, exclusions from the waiting list included both death or OLT, contraindications derived from tumour progression (vascular invasion, lymph node involvement, or metastases), or liver functional impairment (that is, progressive hepatorenal syndrome).

The probabilities for dropout rate assumed in the model are summarised in table 1. For the treated groups, values were derived from probabilities of survival and recurrence after resection and PEI. Patients who presented recurrences were considered for exclusion when they developed major contraindications. Data for the non-treatment arm were derived from the reported probability of tumour progression, vascular invasion, and extrahepatic spread, taking into account that HCC progression does not always prompt exclusion from the list. Once exclusion of the list had occurred, median survival was modelled to be less than one year.[27]

Outcomes of patients effectively transplanted were obtained from the best results of groups applying restrictive selection criteria. In the reference case, five year survival after OLT and recurrence rate were 70% and 10%, respectively.[4 6–8]

Sensitivity analysis

As previously described, for the two reference cases the probabilities of survival during the waiting list (with or without

Table 1 Summary of assumptions used in the Markov analysis

Variable	Actuarial survival (months)			
	6	12	18	24
Surgical resection*				
Actuarial probability of survival	93%	93%	83%	75%
Actuarial probability of dropout	8%	10%	17%	30%
Actuarial probability recurrence	9%	19%	25%	30%
Three month related mortality—4%				
Percutaneous treatment**				
Actuarial probability of survival	95%	86%	76%	65%
Actuarial probability of dropout	10%	20%	35%	50%
Actuarial probability recurrence	7%	18%	21%	25%
Complete response				
Single HCC <3 cm—80%				
Single HCC 3–5 cm—50%				
Three nodules <3 cm—40%				
Natural history*/**				
Actuarial probability of survival	97%	80%	72%	65%
Actuarial probability of dropout				
Group 1	7%	15%	30%	50%
Group 2	18%	36%	50%	70%
Probability of growth of main nodule, 1 year—70%				
Probability of vascular invasion, 1 year— 21%				
Probability of extrahepatic spread, 1 year—9%				
Liver transplantation				
Global outcome after OLT, 5 year survival—70%				
Probability of recurrence, 5 year—10%.				
Three month related mortality—2%				
Probability of survival after dropping out while on the waiting list according to the study groups				
Group 1	60%	40%	32%	16%
Group 2	40%	20%	10%	0%

*Reference case No 1 (group 1).
**Reference case No 2 (group 2).

treatment), dropout rate, and survival after transplantation are shown in table 1. The sensitivity analysis was applied to test different degrees of estimates of the various probabilities used.[19 20] Establishment of two strata represents a type of sensitivity analysis of the scenarios that are faced in the clinical setting. None the less, additional sensitivity analyses were performed varying the main probabilities of outcomes over clinically relevant ranges.

Variables modelled in the sensitivity analysis included the dropout rate and outcome after OLT.

(1) *Variations in the dropout rate*. (a) Best scenario: treatment achieves a relative reduction of 20% in the dropout rate from the reference case of the treatment arm. (b) Worst scenario: treatment achieves a relative increase of 20% in the dropout rate from the reference case of the treatment arm.

(2) *Variations in outcome of transplantation*. Survival after OLT was modelled to include a five year survival rate as low as 50% as the worst scenario.

Costs

Economic costs were assessed from the payer's perspective, and included direct costs of procedures and treatments, expressed in 1999 US dollars, and were obtained from the current payments within the Spanish Health Care System (table 2). These cover the cost of salaries for physicians, surgeons, and support personnel, equipment, supplies, and organisational costs. Direct non-medical costs incurred by patients and their families, as well as indirect costs, were not assumed in the analysis. Future costs and benefits were discounted at a baseline rate of 3%.[19 20]

Table 2 Direct costs for procedures and treatments

Variable	Mean baseline cost (US$)
Direct cost of procedures	
Analytical data and imaging techniques	
Analytical data (including AFP)	80
Doppler ultrasound	113
Spiral computed tomography scan	266
Bone scintigraphy	100
Treatments	
Surgical resection	13 330
Percutaneous ethanol injection	3990
Orthotopic liver transplantation	73 330
Follow up while on waiting list	
After resection	
First year	1000
Second year	4000
After percutaneous ethanol injection	
First year	4830
Second year	9330
After dropout	
First year	8130
Second year	13 065
Follow up after OLT	
First year	26 660
Second year and thereafter	13 330
Outcomes	
HCC related terminal care	6660
Death after OLT	13 330

OLT, orthotopic liver transplantation; HCC, hepatocellular carcinoma.

Estimates of effectiveness and cost effectiveness

We considered a 10% increase in the probability of being transplanted as clinically relevant. Effectiveness was measured as net gain in life expectancy (LE), and according to recent proposals we defined an increase of at least three months in LE as clinically relevant.[28] Although quality of life is an important outcome in calculating cost effectiveness, reliable data on HCC patients waiting for a liver donor are not available and thus this analysis was not addressed.[29] The marginal cost of the treatment strategy was divided by its incremental benefit, as measured by gain in LE. This results in a marginal cost per years of life saved (MCYLS) and we have

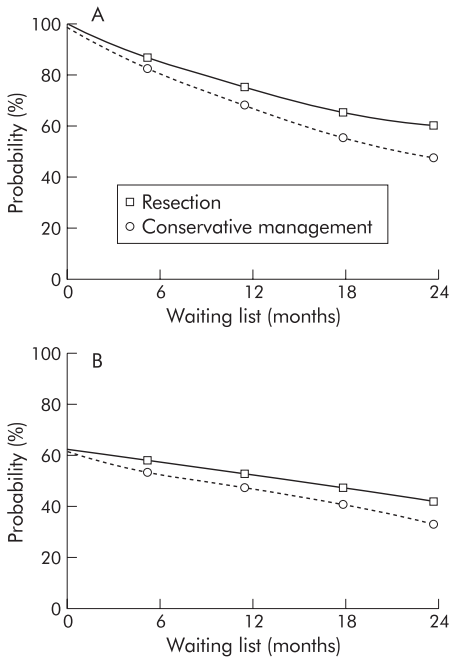

Figure 2 Probability of being transplanted (A) and seven year intention to treat survival (B) comparing patients with hepatocellular carcinoma undergoing resection versus conservative management while on the waiting list for liver transplantation.

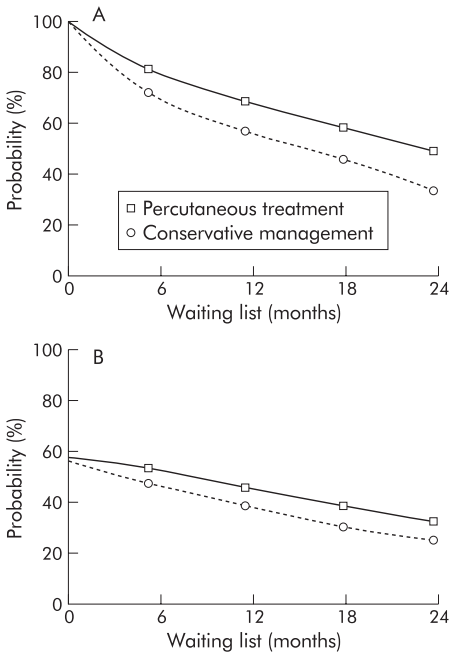

Figure 3 Probability of being transplanted (A) and seven year intention to treat survival (B) comparing patients with hepatocellular carcinoma undergoing percutaneous treatment versus conservative management while on the waiting list for liver transplantation.

applied the conventional threshold of $50 000 per year of life saved as the accepted cut off value to consider an intervention "cost effective".[30–34]

RESULTS

Probability of being transplanted and overall survival

The probability of being transplanted and the overall survival are depicted in figs 2 and 3. Surgical resection increased the transplantation rate from 3.7% to 10.7% for waiting lists of six and 24 months, respectively. The seven year probability of survival increased for patients undergoing resection compared with standard management, and was higher than 10% for waiting lists exceeding one year. Percutaneous treatments increased the probability of being transplanted and the seven year survival in all waiting times. These benefits became clinically relevant when the waiting time exceeded one year.

Cost effectiveness

The results of the CEA are shown in figs 4 and 5, and table 3. Resection provided a clinically relevant net gain in LE ranging from 4.8 to 6.1 months if waiting times exceeded six months. The CEA shows that the MCYLS was less than $40 000 for lists of 12–24 months. Ethanol injection achieved a clear gain in LE, ranging from 5.2 to 6.7 months, increasing according to the length of the waiting list. Its cost effectiveness ratio was less than $23 000/year of life saved (fig 5). Undiscounted results did not statistically differ from those discounted at 3%.

Sensitivity analysis

The results of the sensitivity analysis are shown in table 4. Our model was most sensitive to variations in the dropout rate and survival after OLT. When assuming the highest benefit as a result of treatment (best scenario: relative decrease of 20% in dropout rate), gains in LE were relevant (resection 3.3–8.3 months; PEI 6.8–9.1 months), with a cost effectiveness ratio always below $60 000/year of life saved. When considering scenarios of poor outcome after resection (worst scenario: relative increase of 20% in dropout rate), this treatment provided a minimal benefit in LE, with a marginal cost ranging from $135 600/year of life saved (six month waiting list) to

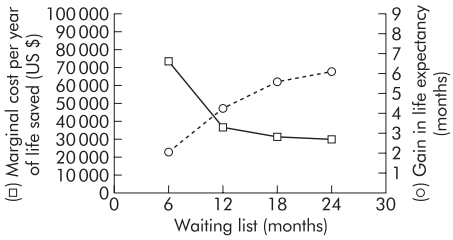

Figure 4 Cost effectiveness analysis of surgical resection for hepatocellular carcinoma versus conservative management while on the waiting list for liver transplantation. Cost effectiveness ratio and marginal effectiveness in terms of gains in life expectancy are shown according to length of waiting time.

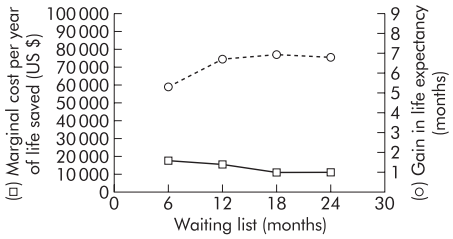

Figure 5 Cost effectiveness analysis of percutaneous treatments for non-surgical hepatocellular carcinoma versus conservative management while on the waiting list for liver transplantation. Cost effectiveness ratio and marginal effectiveness in terms of gains in life expectancy are shown according to length of waiting time.

$43 650/year of life saved (24 month waiting list). Conversely, even in this worst scenario, PEI offered gains in LE always exceeding three months, with a marginal cost per year of life of less than $32 000.

Assuming a 50% five year survival rate after OLT (worst scenario), the estimates of LE decreased in all cases. For this scenario, PEI retained a cost effectiveness ratio for all waiting times but resection was cost effective only for waiting times exceeding two years ($43 074/MCLYS).

Table 3 Cost effectiveness analysis of performing adjuvant therapy according to risk group and length of waiting list

Risk group	Waiting list scenario	Gain in LE (months)	MCYLS (US$)
Group 1	6 m	2.2	74 728
	12 m	4.8	38 117
	18 m	5.9	32 886
	24 m	6.1	32 060
Group 2	6 m	5.2	16 442
	12 m	6.5	12 489
	18 m	6.7	10 911
	24 m	6.4	10 086

MCYLS, marginal cost per year of life saved.

Table 4 Sensitivity analysis for the best and worst scenarios of dropout rate and survival after orthotopic liver transplantation (OLT) according to risk group and length of waiting time (range 6–24 months)*

Scenario	Gain in LE (months)	MCYLS (US$)
Group 1		
Best dropout rate**	3.3–8.3	54 291–27 362
Worst dropout rate***	1.1–4.2	135 639–43 650
Five year survival after OLT (50%)	1.5–4.6	103 007–43 074
Group 2		
Best dropout rate**	6.8–9.1	16 536–11 690
Worst dropout rate***	3.8–4.3	19 593–10 509
Five year survival after OLT (50%)	2.0–4.7	42 105–13 824

*All results are expressed according to the waiting time range: the first figure corresponds to six months–the last figure corresponds to 24 months of waiting time.
**20% decrease in dropout rate compared with reference case, as a result of treatment
***20% increase in dropout rate compared with reference case, despite treatment.
MCYLS, marginal cost per year of life saved.

DISCUSSION

The excellent results of liver transplantation for early HCC are curtailed by the increasing dropout rate while waiting for a donor, thus worsening outcome when analysed on an intention to treat basis.[1 4] Several strategies have been postulated to decrease the impact of exclusions. Living donor liver transplantation, domino and split liver transplantation, as well as use of marginal livers are policies currently applied in some transplant units. A decision analysis has recently shown that living donor liver transplantation compared with OLT is cost effective for early HCC for waiting times exceeding seven months.[35] However, implementation of these strategies is complex, and will probably be restricted to leading transplant units. This has led most centres to administer antitumoral treatments on entering HCC patients onto waiting lists.[13–18] The benefits of this policy are unknown as prospective RCTs in the field are lacking and they are seen as almost unfeasible due to the cost, heterogeneity, and complexity of the medical interventions. This uncertainty prompted us to conduct a decision analysis to address the clinical benefits and cost effectiveness of adjuvant treatment.

The model applies the best curative therapies available for the selected strata of HCC candidates for OLT and considers a waiting time between six and 24 months. This strategy predicts moderate gains in LE in almost all cases, and the gain remains below the accepted cost effectiveness ratio ($50 000/per year of life saved).[30–34] In fact, it compares favourably with accepted medical interventions, such as implantable cardioverter-defibrillator for coronary heart disease ($26 000–40 000 per year of life) or haemodialysis ($42 000/quality adjusted life year saved).[32–34] Surgical resection was cost effective while waiting for at least one year. After this time, surgery increased the transplantation rate, with moderate gains in LE and an acceptable cost effectiveness ratio. In contrast, LE gains and cost effectiveness ratio were less favourable ($74 000 per year life gained) with shorter waiting times. There may be some concerns on the applicability of this invasive therapy while on the waiting list. As an alternative, primary liver resection and "salvage OLT" (performed when recurrence or decompensation after resection occurs) have been postulated to save organs.[36] We have applied this policy over the last decade, where resection was considered as the firstline option, but unfortunately less than 10% of candidates benefited.[1]

Surgery is feasible for patients with preserved liver function and single tumours but it is too risky in subjects with impaired hepatic function and/or multiple HCC sites.[2–5] Their high morbidity and mortality impede any benefit of surgery. Accordingly, these patients were modelled to receive percutaneous treatment, which was identified as cost effective in all scenarios. It could be argued that PEI is not the sole effective therapy for non-surgical HCC and that other widely used alternatives such as RF thermal ablation,[26 37] chemoembolisation,[13–18] or even chemotherapy[38] could be modelled. Ethanol injection is a safe, cheap, and effective treatment that achieves a 40–80% response for patients with small HCC[21–24] and the available studies provide robust information for decision analysis. RF thermal ablation as a primary treatment for HCC may have similar efficacy.[37] Compared with PEI, its increased cost and the impact of complications may balance the benefits of reduced hospital stay. However, we have recently reported a 10% rate of tumour seeding after RF thermal ablation associated with subcapsular location or an aggressive tumoral pattern. Therefore, although there are no studies on its benefit when applied during the waiting list, we discourage this procedure prior to OLT.[26] Finally, chemoembolisation is the standard antitumoral treatment for HCC prior to OLT in most transplant programs. Its antitumoral effect, even when using high dose chemotherapy, is less than that of PEI, and despite the fact that some authors have suggested benefits in patients with a favourable response to therapy (downstaging),[13] there are no RCTs showing the benefit of this strategy. In addition, studies assessing this point have not identified a difference in tumour recurrence and survival attributable to therapy.

The sensitivity analysis disclosed that ethanol injection was beneficial and cost effective in all ranges used but the benefits of resection decreased when varying the assumptions of the model. In the worst scenarios for dropout rate and survival after OLT (five year survival 50%), resection provided poor gains in LE regardless of the length of the waiting list, with an expensive cost effectiveness ratio. These controversial benefits may be representative of transplantation centres achieving poor results after surgery as a consequence of both limited technical skills and expertise of the group. In support of this, it has recently been reported that OLT centres in the USA that perform less than 20 transplantations per year have mortality rates higher than those at larger centres.[39] Thus decision makers should consider these data to warrant implementation of economic resources for the most efficient groups. As done for most decision analyses, we used local costs for cost effectiveness estimations. However, it is clear that health costs in Southern Europe are lower than in Northern countries or even in the USA. Accordingly, in areas where local economics are largely higher, the cost effectiveness of some scenarios may be lost.

The current analysis was limited by the scarcity of data on exclusions during the waiting list. For untreated patients we have assumed a dropout rate ranging from 15% to 36% at one year of waiting time, for the two reference cases. In the sensitivity analysis, these values varied by 20% up/down in the

best/worst scenarios. These assumptions were derived from our reported data on exclusions, and are in accordance with recent 1999 data from the UNOS, where patients removed from the list due to death or other reasons in the USA ranged from 26% to 41%.[9]

In summary, our study indicates that adjuvant treatment on entering HCC patients onto a waiting list for OLT is cost effective and recommended in almost all scenarios. Patients with well preserved liver function and a single HCC, waiting for at least one year, may benefit from surgical resection but for shorter waiting times the economic investment is controversial. In non-surgical patients, percutaneous treatments are cost effective in all waiting times and thus their application is warranted.

ACKNOWLEDGEMENTS

Supported by grant SAF 004-98 from the Comisión Interdepartamental de Ciencia y Tecnología, and a grant from the Fundació La Marató TV3, 1999.

Authors' affiliations

J M Llovet, J Fuster, M Navasa, J Rodés, J Bruix, Barcelona-Clínic Liver Cancer (BCLC) Group, Liver Unit, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), Hospital Clínic, University of Barcelona, Catalonia, Spain
X Mas, J J Aponte, Epidemiology-Biostatistics Unit, Institut d'Investigacions Biomèdiques August Pi I Sunyer, Hospital Clínic, University of Barcelona, Catalonia, Spain
E Christensen, Clinic of Internal Medicine, Bispebjerg University Hospital, Copenhagen, Denmark

REFERENCES

1 **Llovet JM**, Bruix J, Gores GJ. Surgical resection versus transplantation for early hepatocellular carcinoma: clues for the best strategy. *Hepatology* 2000;**31**:1019–21.
2 **Bruix J**, Castells A, Bosch J, *et al*. Surgical resection of hepatocellular carcinoma in cirrhotic patients. Prognostic value of preoperative portal pressure. *Gastroenterology* 1996:**111**;1018–22.
3 **The Liver Cancer Study Group of Japan**. Predictive factors for long term prognosis after partial hepatectomy for patients with hepatocellular carcer in Japan. *Cancer* 1994;**74**:2772–80.
4 **Llovet JM**, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology* 1999;**30**:1434–40.
5 **Makuuchi M**. Surgical treatment for hepatocellular carcinoma. In: Arroyo V, Bosch J, Rodes J, eds. *Treatments in hepatology*. Barcelona: Masson, 1995:341–52.
6 **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**:693–9.
7 **Llovet JM**, Bruix J, Fuster J, *et al*. Liver transplantation for treatment of small hepatocellular carcinoma: the tumor-node-metastasis classification does not have prognostic power. *Hepatology* 1998;**27**:1572–7.
8 **Bismuth H**, Majno PE, Adam R. Liver transplantation for hepatocellular carcinoma. *Semin Liver Dis* 1999;**19**:311–22.
9 **United Network for Organ Sharing**. Annual report 1999. Http://www.unos.org/data.
10 **Memoria de la actividad de donación y transplante 1997**. Organización Nacional de Transplantes. Madrid: Centro de Publicaciones del Ministerio de Sanidad y Consumo, 1997.
11 **Pereira SP**, Williams R. Limits to liver transplantation in UK. *Gut* 1998;**42**:883–5.
12 **Schwartz M**, Sung M, Emre S, *et al*. Liver transplantation for hepatocellular carcinomas > 5 cm diameter: results of a multimodality protocol. *Abstracts of the 23rd Annual Meeting of the American Society of Transplant Surgeons,* Chicago, May 1997. Washington, DC: American Society of Transplant Surgeons, 1997.
13 **Majno PE**, Adam R, Bismuth H, *et al*. Influence of preoperative transarterial lipiodol chemoembolization on resection and transplantation for hepatocellular carcinoma in patients with cirrhosis. *Ann Surg* 1997;**226**:688–701.
14 **Heneghan MA**, O'Grady JG. Liver transplantation for malignant disease. *Baillieres Best Pract Res Clin Gastroenterol* 1999;**13**:575–91.
15 **Oldhafer KJ**, Chavan A, Fruhauf NR, *et al*. Arterial chemoembolization before liver transplantation in patients with hepatocellular carcinoma: marked tumor necrosis, but no survival benefit? *J Hepatol* 1998;**29**:953–9.
16 **Venook AP**, Ferrell LD, Roberts JP, *et al*. Liver transplantation for hepatocellular carcinoma: results with preoperative chemoembolization. *Liver Transpl Surg* 1995;**1**:242–8.
17 **Olthoff KM**, Rosove MH, Shackleton CR, *et al*. Adjuvant chemotherapy improves survival after liver transplantation for hepatocellular carcinoma. *Ann Surg* 1995;**221**:734–41.
18 **Harnois DM**, Steers J, Andrews JC, *et al*. Preoperative hepatic artery chemoembolization followed by orthotopic liver transplantation for hepatocellular carcinoma. *Liver Transpl Surg* 1999;**5**:192–9.
19 **Russell LB**, Gold MR, Siegel JE, *et al*. The role of cost-effectiveness analysis in health and medicine. Panel on cost-effectiveness in health and medicine. *JAMA* 1996;**276**:1172–7.
20 **Siegel JE**, Weinstein MC, Russell LB, *et al*. Recommendations for reporting cost-effectiveness analyses. Panel on cost-effectiveness in health and medicine. *JAMA* 1996;**276**:1339–41.
21 **Vilana R**, Bruix J, Brú C, *et al*. Tumor sizes determines the efficacy of percutaneous ethanol injection for treatment of small hepatocellular carcinoma. *Hepatology* 1992;**16**:353–7.
22 **Ishii H**, Okada S, Nose H, *et al*. Local recurrence of hepatocellular carcinoma after percutaneous ethanol injection. *Cancer* 1996;**77**:1792–6.
23 **Livraghi T**, Giorgio A, Marin G, *et al*. Hepatocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. *Radiology* 1995;**197**:101–8.
24 **Castellano L**, Calandra M, Del Vecchio Blanco C, *et al*. Predictive factors of survival and intrahepatic recurrence of hepatocellular carcinoma in cirrhosis after percutaneous ethanol injection: analysis of 71 patients. *J Hepatol* 1997;**27**:862–70.
25 **Di Stasi M**, Buscarini L, Livraghi T, *et al*. Percutaneous ethanol injection in the treatment of hepatocellular carcinoma. *Scand J Gastroenterol* 1997;**32**:1168–73.
26 **Llovet JM**, Vilana R, Brú C, *et al*. Increased risk of tumor seeding after radiofrequency thermal ablation for single hepatocellular carcinoma. *Hepatology* 2001;**33**:1124–9.
27 **Llovet JM**, Bustamante J, Castells A, *et al*. Natural history of untreated non-surgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* 1999;**29**:62–7.
28 **Wright JC**, Weinstein MC. Gains in life expectancy from medical interventions—standardizing data on outcomes. *N Engl J Med* 1998;**339**:380–6.
29 **Bravata D**, Olkin I, Barnato A, *et al*. Health-related quality of life after transplantation: A meta-analysis. *Liver Transpl Surg* 1999;**5**:318–31.
30 **Laupacis A**, Feeny D, Detsky AS, *et al*. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations *Can Med Assoc J* 1992;**146**:473–81.
31 **Hayman J**, Hillner B, Harris J, *et al*. Cost-effectiveness of routine radiation therapy following conservative surgery for early-stage breast cancer. *J Clin Oncol* 1998;**16**:1022–9.
32 **Tengs TO**, Adams ME, Pliskin JS, *et al*. Five-hundred life-saving interventions and their cost-effectiveness. *Risk Anal* 1995;**15**:369–90.
33 **Kuntz KM**, Lee TH. Cost-efectiveness of accepted measures for intervention in coronary heart disease. *Coronary Artery Dis* 1995;**6**:472–8.
34 **Smith TJ**, Hillner BE, Desch CE. Efficacy and cost-effectiveness of cancer treatment: Rational allocation of resources based on decision analysis. *J Natl Cancer Inst* 1993;**85**:1460–74.
35 **Sarasin F**, Majno P, Llovet JM, *et al*. Live donor liver transplantation for early hepatocellular carcinoma: a cost-effectiveness perspective. *Hepatology* 2001;**33**:1073–9.
36 **Majno P**, Sarasin F, Mentha G, *et al*. 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.
37 **Livraghi T**, Goldberg SN, Lazzaroni S, *et al*. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. *Radiology* 1999;**210**:655–61.
38 **Stone MJ**, Klintmalm GB, Polter D, *et al*. Neoadjuvant chemotherapy and liver transplantation for hepatocellular carcinoma: a pilot study in 20 patients. *Gastroenterology* 1993;**104**:196–202.
39 **Edwards EB**, Roberts JP, McBride MA, *et al*. The effect of the volume of procedures at transplantation centers on mortality after liver transplantation. *N Engl J Med* 1999;**341**:2049–53.