Transplant International

Transplant International ISSN 0934-0874

REVIEW

Liver transplantation for primary and metastatic liver cancers

Emir Hoti[1,2] and Rene Adam[1,3,4]

1 AP-HP Hôpital Paul Brousse, Centre Hépato-Biliaire, Villejuif, France
2 Liver Transplant Unit, Saint Vincent's University Hospital, Elm Park Dublin 4, Ireland
3 Université Paris-Sud, UMR-S 785, Villejuif, France
4 Inserm, Unité 785, Villejuif, France

Keywords
cholangiocarcinoma, hepatocellular carcinoma, liver metastases.

Correspondence
Professor Rene Adam, AP-HP Hôpital Paul Brousse, Centre Hépato-Biliaire, 12 Avenue Paul Vaillant Couturier, F-94804 Villejuif, France. Tel.: +33145593049; fax: +33145593857; e-mail: rene.adam@pbr.aphp.fr

Received: 21 April 2008
Revision requested: 9 May 2008
Accepted: 25 June 2008

doi:10.1111/j.1432-2277.2008.00735.x

Summary

Liver transplantation for hepatic malignancies has emerged as a well-documented and proven treatment modality. However, early unsatisfactory results emphasized that only a highly selected patient population would benefit from transplantation. Currently, 15% of all liver transplants performed are for hepatocellular carcinoma (HCC). There is no controversy about the fact that liver transplantation for HCC in the adult population yields good results for patients whose tumour masses do not exceed the Milan criteria. It remains to be determined whether patients with more extensive tumours can be reliably selected to benefit from the procedure. In patients with small HCC at an early stage and preserved liver function, liver resection provides an alternative to transplant. Liver resection may offer similar survival results to orthotopic liver transplantation (OLT) in the short term, and does not carry the long-term effects of immunosuppression; however, long-term and disease-free survival favours liver transplantation. Very promising results have been obtained for cholangiocarcinoma treated by aggressive combination therapies, including chemo- and radiotherapy followed by OLT. Survival rate in these selected patients can approach that of patients with cholestatic liver disease, and the role of transplantation now requires re-evaluation. Similarly, hepatoblastoma is an excellent indication in paediatric patients with unresectable or recurrent tumours. Epithelioid hemangioendothelioma is also an appropriate indication for liver transplantation, even in the presence of extrahepatic metastases, unlike angiosarcoma which is associated with a very poor survival and considered as a contraindication. And finally for metastatic liver disease from neuroendocrine tumours, liver transplantation can result in long-term survival and even cure in well selected patients. Conversely, the value of transplantation for colorectal liver metastases (currently a contraindication) requires further evaluation by well-designed trials.

Introduction

Since the late 1990s, orthotopic liver transplantation (OLT) has been established as a durable treatment for all forms of end-stage liver disease as well as for hepatocellular carcinoma (HCC). Transplantation is conceptually a very attractive treatment option particularly for patients with malignant liver disease because it eliminates both detectable and nondetectable tumour nodules present in the cirrhotic liver. In addition, it simultaneously treats the underlying liver cirrhosis and prevents complications of the associated portal hypertension. Although initial

OLT outcomes were disappointing, better results have been progressively obtained by refining the patients' selection criteria. The work conducted initially by Bismuth *et al.* [1] and subsequently by Mazzaferro *et al.* [2], established selection guidelines, which currently are still in use for identifying the subgroup of HCC patients who would maximally benefit from the liver transplant in term of survival rate. A recent 3-year survival data from United Network for Organ Sharing (UNOS) for patients transplanted for malignant liver pathology showed a survival rate of 70%, compared to survival of 78.3% for other indications, clearly demonstrating the progress made. The success obtained in the treatment of HCC by OLT has also influenced the treatment of other liver malignancies. Liver transplantation, which nowadays is a routine procedure, can be used also for tumours such as cholangiocarcinoma, epithelioid hemangioendothelioma, neuroendocrine tumour metastases and hepatoblastoma. Although, certain criteria have been developed for these less common tumours producing satisfactory survival results, controversies still exist and to this end, tumour characteristics such as pathology, size, lobar distribution and stage are extensively being studied to select the optimal treatment option. The purpose of this article was to review the status of the OLT for primary and secondary hepatic malignancy.

Hepatocellular carcinoma

The earlier disappointment about the poor outcome of patients who received liver transplantation (OLT) for HCC led most transplant centres during the years to a plethora of studies attempting to find innovative surgical strategies. Overlooking more than a decade of experience with different attempts to improve OLT results, two studies emerged as the most prominent among others. The study conducted by our team in 1993 [1], was the first one to develop a patient-selection strategy, from which the current selection guidelines have evolved. Selecting patients with tumours ≤3 cm and ≤3 lesions for transplantation, led to a reversal of the traditional policy of 'transplanting unresectable HCC' to that of 'transplanting resectable HCC', which in turn resulted in an improved survival post-LT.

The prospective trial (validated by explant pathology) conducted by Mazzaferro *et al.* [2], on the other hand, emerged as the most successful study in establishing the selection criteria. In his landmark study (published in 1996), Mazzaferro reported an improved survival- and reduced recurrence rates post-OLT with the use of what became known as the Milan Criteria, which incorporated cirrhotic patients with up to three lesions with the largest being ≤3 cm, or patients with a single HCC lesion ≤5 cm. With a demonstration of 5-year and recurrence-free survival exceeding 70% and 83%, respectively, the majority of the transplant units worldwide including the UNOS [3] adopted and currently use the Milan criteria to direct patient selection for LT.

Although, the wide acceptance of these criteria has been associated with definite improvements in patients' survival (5-year survival 70%; European Liver Transplant Registry (ELTR) [4]), their staging value is limited by the current imaging techniques, resulting in a higher exclusion rate from transplantation of patients with borderline lesions. Taking into consideration the fact that nearly a third of the patients who undergo transplantation for HCC fall outside the criteria on the basis of pathological findings in the explanted livers [2,5], transplant centres [6] came with the suggestion of expanding the selection criteria to offer OLT to a broader group of patients with HCC. Perhaps, the most interesting study which generated much interest and also controversies came from Yao *et al.* [6] at the University of California, San Francisco (UCSF). In 2001, the author reported that modest expansion of the tumour size limits beyond Milan criteria did not adversely impact the survival after OLT (5-year survival 75% for lesions ≤6.5 cm or with cumulative size ≤8 cm). The proposed expanded criteria (Table 1) were developed using explant pathological data. Subsequent evaluation studies produced similar results, supporting the view that moderate criteria expansion does not impact the survival adversely [7,8]. However, because of the small sample size and use of retrospective explant tumour pathology, the results of these studies were challenged and also several groups advised caution in expanding the criteria. Recognizing the inherent limitations of the initially published data, Yao *et al.* [9] in a recently published study (2007) went on to evaluate his proposed criteria based on preoperative imaging, going back as far as year 2001. The results showed that in 168 patients meeting the UCSF criteria, the 1- and 5-year recurrence-free probabilities were 95.9% and 90.9%, and the respective survivals without recurrence were 92.1% and 80.7%. Understaging of the tumour (explant findings) ranged

Table 1. Milan and UCSF staging criteria for hepatocellular carcinoma.

		Multiple tumours		
Staging	Single tumour lesion	Maximum no. of lesions	Size of the largest tumour lesion	Cumulative maximal tumour size
Milan	≤5 cm	3	≤3.0 cm	NA
UCSF	≤6.5 cm	3	≤4.5 cm	≤8 cm

NA, not applicable.

between 20% and 29%, confirming again the earlier findings that UCSF criteria are suitable as selection criteria for OLT, with similar risk of tumour recurrence and understaging to the Milan criteria. Similar finding had been reported in an earlier study by Sotirpoulops *et al.* [10], which demonstrated that the accuracy of pretransplant staging of UCSF criteria was the same as the Milan criteria. In a recent study conducted by Duffy *et al.* [11], (the largest from a single institution) involving 467 patients, outcomes of three groups of patients were compared, (group 1: fulfilled Milan criteria; group 2: fulfilled UCSF criteria but not Milan; group 3: exceeded UCSF criteria). No significant 5-year survival difference was found between patients who met Milan and UCSF criteria, based on preoperative imaging (64% vs. 79%) and also on pathological examination (71% vs. 86%). In contrast, the 5-year survival of the group who did not meet the UCSF criteria was much lower (<50%). Likewise, comparable findings were reported by different authors [12–14]. Conversely, a French report [15] including 461 patients, the intention-to-treat analysis showed that the 5-year survival of the patients within UCSF criteria was 46% as compared to 60% of the patients within Milan criteria, prompting the investigator to suggest that the expanded criteria should not be used. Although, the evidence continues to support the moderate expansion of the existing Milan criteria (Table 2), to date, findings from different studies are not always consistent, without strong statistical power, and most importantly lack a prospective validation by pretransplant imaging.

As to the question whether these criteria can safely be applied, the current opinion still remains divided with groups already using the UCSF criteria and others maintaining a 'status quo' and is unlikely that this situation will change in the near future, as prospective evaluation studies need to be done. Nevertheless, the opinion of some authors [16,17] would suggest that the decision to expand the criteria depends upon what the transplant groups would accept as an acceptable survival after OLT for HCC. In a previously published review by the co-author of this paper [16], a 5-year survival of 50% was suggested as the lowest acceptable criteria. Thus, selecting such cut-off level would certainly influence the decision in favour of criteria expansion, given the fact that the results of UCSF criteria have already exceeded this cut-off level.

Certainly as more centres opt to adopt the new expanded criteria, the number of patients with HCC for transplantation will increase. Based on the UCSF data, the number of HCC patients is estimated to increase by a further 30% [18]. This change constitutes a problem as it will strain further the existing donor supply, consequently impacting the waiting time and drop-out rate (20%–30%) of the patients already in the waiting lists [19,20]. Delay to transplantation can significantly reduce the intention-to-treat survival of patients to 60% at 2–3 years [19,20]. As a way to deal with the increase in the number of patients, living donor liver transplant (LDLT) has been advocated. At the present time, the use of living donors is justified by the critical shortage of deceased donor organs and the reduced probability of receiving deceased donor transplantation by nonurgent patients. This technique certainly has had an impact in Asian countries, where LDLT constitutes the bulk of the transplantations caused by a shortage of deceased donors. In theory, LDLT is advantageous because of a better overall status of the recipient, better graft function as well as a shorter waiting time, hence eliminating the risk of tumour progression and also the need for neoadjuvant therapy. Despite the lack of long-term data supporting superior survival outcomes or lower HCC recurrences with earlier LDLT compared to deceased donor liver transplantation (DDLT), evidence from ELTR (unpublished data) has revealed that LDLT performed in

Table 2. Liver transplantation results for HCC using Milan and expanded criteria.

		Number of patients			1-year survival (%)		5-year survival (%)	
Author	Year	Total	Milan	Expanded	Milan	Expanded	Milan	Expanded
Yao *et al.*	2002	70	46	24	91	71	72	57
Fernandez *et al.*	2003	53	33	20	82	75	68	54
Marsh/Dvorchik	2003	393	248	145	–	–	67	–
Ravaioli *et al.*	2004	63	55	8	90	76	78	38
Leung *et al.*	2004	144	74	14	86	–	51	–
Todo/Furukawa	2004	316	138	171	81	75	78	60
Hwang *et al.*	2005	213	151	62	–	–	91	63
Decaens *et al.*	2006	479	279	188	80	78	60	46
Onaca *et al.*	2007	1206	631	575	85	67	62	43
Duffy *et al.*	2007	467	173	294	91	88	79	64

HCC, hepatocellular carcinoma.

European transplant centres has produced similar 4-year survival rates compared to the DDLT. Also, experiences from transplant groups [21] have reported that the LDLT is superior to DDLT for patients with HCC within Milan criteria who wait longer than 7 months. A report from Japan involving 316 patients showed 1- and 3-year recurrence-free survival rates of 72.7% and 64.7%, respectively [22]. Patients who met the Milan criteria had a survival and disease-free survival of 78.8% and 79.1% respectively, higher than the same in those patients who did not (60.4% and 52.6%) [22]. The experience of LDLT in Western countries has been somehow different. Trotter *et al.* [23], in a study found that the current donor acceptance rate is 40%. The rate has dropped over time, which is probably because of the negative influence exerted by highly publicized mortality (0.3–1%; 19 donor deaths over a 17-year period) [24] and morbidity (14–35%) encountered among the donors [25]. In Europe, the current donor mortality is 0.27% and overall postoperative morbidity is 15%, increasing to 18% for the right lobe donation (ELTR Report). Also, the institution of the model for end-stage liver disease (MELD) score as the basis for the DDLT may have influenced the use of LDLT. Following the MELD introduction in February 2002, fewer patients died in the waiting list, likely because of the expedited DDLT. Certainly, observations have shown that higher numbers of LDLT candidates are receiving DDLT during the course of the donor evaluation.

Further controversy which has fuelled more discussion nowadays among transplant teams comes from attempts to use live donors for patients with indications beyond Milan and UCSF criteria. Although, this opinion has supporters among Asian surgeons [22], the problem of an as yet limited data makes the claimed survival benefits of this approach questionable, indicating that further studies are required to answer this issue. As with the use of LDLT for the above indication, the appropriateness to perform LDLT for patients with small HCC and preserved liver function has generated much debate. There is evidence [26] supporting the transplantation, with reports of very good outcomes following the introduction of Rapamycin (Sirolimus), which has demonstrated anti-tumoural and immunosuppressive activities [27]. On the other hand, there are a number of groups treating HCC patients with preserved liver function with resection, achieving a 5-year survival of 70% [28]. Indeed, multiple studies comparing resection to transplantation in patients with Child's A disease have shown tumour-free and long-term survival is superior in the transplanted patients in addition to the fact that transplant also cures the underlying liver cirrhosis. Intention-to-treat analyses, however, have demonstrated that the superiority of the OLT over hepatic resection diminishes with increasing waiting time [19,20]. As a result, many centres actively treat patients with HCC prior to OLT with the aim to reduce the tumour progression and waiting list drop-out. Although, a number of pre-OLT ablative interventions have been advocated [transarterial chemoembolization (TACE), Percutaneous Ethanol injection, radiofrequency ablation (RFA)], the benefits of these bridging therapies remains to be proven, preferably by controlled randomized trials. Nevertheless, some authors [29–31] seem to support the percutaneous RFA of tumour as the most effective intervention for patients with lesions ≤3 cm in diameter, achieving a up to 63% complete response on the explant examination. At the present time, it would seem that the advantages of liver transplant over the resection depend on the transplant policies of the liver units, their organ allocation system and waiting time. Not surprisingly, many centres agree to transplant patients with impaired liver function, cirrhosis, portal hypertension and small HCC, reserving the resection for the group of patients with an expected long-term survival, mainly those with small HCC and no portal hypertension. However, the later approach is much more influenced by a pragmatic decision related to organ shortage, rather than by the apparent equal survival results of these two treatment modalities.

Another suggested approach to reduce the donor shortage is liver resection followed by transplantation, if patients develop tumour recurrence. Such strategy is based on the assumption that if recurrence develops after the resection, patient will be transplantable. However, a study conducted by our team, analyzing only patients who were transplanted for tumour recurrence following resection, reached different conclusions on salvage transplantation [32]. To begin with, we found a significantly higher preoperative morbidity and mortality (28.6% for salvage LT versus 2.1% Primary LT) in conjunction with a lower overall and disease-free survival rate (41% Salvage LT versus 61% Primary LT) in the salvage transplantation group. In addition, the study demonstrated that primary liver resection, reduces the chances for rescue transplantation (77% of the patients had recurrences postresection, of which only 23% were transplanted) also for long-term survival in cirrhotic patients with HCC. In contrast, Belghiti *et al.* [33] in a retrospective study comparing two groups of patients who underwent either primary transplantation or secondary transplantation after liver resection found no significant differences between them in terms of perioperative morbidity and mortality, overall and recurrence-free survival rates. They concluded that in selected patients liver resection prior to OLT does not increase mortality and it can be integrated in the treatment strategy for HCC. Hwang *et al.* [34] reported that the results of salvage LDLT were the same as the results

of primary LDLT, particularly for patients within Milan criteria. Unfortunately, from the current available evidence, it is very difficult to determine which strategy is more advantageous and comparing the outcomes of the previous studies is likely to yield ambiguous results, partly because of the fact that the later studies included not only patients who were transplanted for tumour recurrence but also for deteriorating liver function as well as patients with positive margins or satellite nodules. Hence the impact of these results in clinical practice should be considered carefully. Comparable to our observations, other studies [21] have demonstrated low rates of suitability of transplantation following the resection, underscoring the complexity of this approach.

In summary, the evolvement of HCC from being a contraindication to OLT in many transplant centres (early 1990s) to a prioritized condition for donor allocation under the MELD is a testament to the progress made in its management so far. There is no doubt that liver transplant (OLT) offers the best chance for cure to unresectable HCC patients with underlying liver dysfunction.

Despite inaccuracies, Milan criteria is the most accurate and efficacious method for patient selection. The proposition to expand the selection criteria has been supported by some studies; however, given their retrospective nature, it is important that any new attempt is to be independently and prospectively validated.

The development of LDLT has the potential to become one of the principal strategies to address the organ shortage. In Asian countries, characterized by a high incidence of HCC and a very low deceased donor rate, it is highly likely that LDLT generates a good benefit, however, its impact in the management of HCC in Western countries requires further evaluation. Regarding the issue of expanding the criteria for LDLT, further studies are needed, preferably with an intention-to-treat basis, taking into account the risk of the donor and the results from alternative treatment in patients with advanced disease. The strategy of liver resection followed by OLT if required, currently is riddled by contradicting issues, involving survival results as well as its suitability as an approach to reduce the need for donor organs.

Cholangiocarcinoma

Cholangiocarcinoma (CCA) is relatively an uncommon malignancy, accounting for 3% of all primary gastrointestinal malignancies and 10% of hepatobiliary malignancies [35]. At present, only surgical excision of all detectable tumour is associated with an improvement in 5-year survival for patients with CCA. However, the surgical contribution is modest, providing a 20–30% 5-year survival for distal lesions and a 9–18% 5-year survival for more proximal lesions [36].

Because of limitations of surgical resection in obtaining adequate margins, liver transplant was proposed as an option for treatment of CCA. Although, numerous groups attempted its use for CCA, because of lack of well-developed treatment protocols and patient selection criteria their initial results were poor, with median survival at less than a year [37,38]. One early report from Penn [39], whose series included 109 patients from different liver transplant centres reported to Cincinnati Transplant Tumour Registry, showed an overall survival of 30% 2 years after transplantation. The Hannover [40] experience of 10 patients with peripheral and 20 patients with central CCA reported similar results, with only 13 patients without regional node disease having a median survival of 35 months and an actuarial survival of 64%. Other groups also, witnessed high recurrence rates and dismal actuarial survival (23% at 5 years) [41–43]. Some centres investigated a multimodality approach for patients with CCA. The Dallas group [44] treated 17 patients with 5-FU and radiotherapy. Both chemo- and radiotherapy were administered 5–9 weeks following liver transplant. However, the results demonstrated a dubious benefit with only three patients found to be alive and without tumour recurrence at 44, 31 and 28 months following the OLT. The survival at 1 year was 53%. The UCLA group reported results of 25 patients transplanted for unresectable CCA. Nine patients received adjuvant postoperative chemotherapy. Overall and disease-free survival rates were 71% and 67% at 1 year and 35% and 32% at 3 years, respectively. In contrast, the 5-year survival of 59 CCA patients in a cohort from Spain [41] was 30% for hilar and 42% for peripheral CCA, respectively (Table 3). The ELTR series, which include patients treated as early as 1985 reported similar survival rates for patients with hilar and peripheral CCA (Table 3).

The results of Pittsburgh [45] group were comparable to other reports (1-year survival 60%, 5-year survival 25%); however, they suggested that the way forward was to develop specific treatment protocols as well as selection criteria. Foo *et al.* [46] described the potential for long-term survival in patients with extrahepatic CCA following external beam radiotherapy and brachytherapy in addition to 5-fluorouracil chemotherapy. This radical approach which involved multiple disciplines led to a different phase in the management of CCA, which is marked by the report of the study conducted in Mayo Clinic [47]. In this pilot study, the use of neoadjuvant chemoradiation followed by OLT resulted in long-term survival in a carefully selected group of patients. The protocol consisted of a combination of external beam radiation, 5-FU infusion and oral capecitabine, as well as intraluminal brachytherapy

Table 3. Liver transplant results for hilar cholangiocarcinoma (CCA).

Author/Institution	Year	No. of patients	Patient survival (%)		
			1-year	3-year	5-year
Bismuth *et al.*	1987	38	40	16 (2-y)	0
O'Grady *et al.*	1988	13	30	10	10
Ringe *et al.*	1996	25	60	21.4	17.1
Iwatsuki *et al.*	1998	27 (LT)	59.3	36.2	36.2
		11 (Cluster)	54.6	9.1	9.1
Bismuth *et al.*	2000	9	–	–	33
DeVreede *et al.*	2000	11	100	100	80
Shimoda *et al.*	2001	25	71		35
Sudan *et al.*	2002	11	–	–	45
Robles *et al.* (multicentre)	2004	36	82	53	30
Ghali *et al.* (multicentre)	2005	10	90	30	–
Rea *et al.*	2005	38	92	82	82
ELTR (Hilar CCA)	2007	270	75	41	30
ELTR (Peripheral CCA)	2007	292	68	35	25

LT, liver transplantation; cluster, abdominal cluster transplantation.

followed by liver transplantation. Exploratory laparotomy prior to transplantation was necessary to confirm stage I or II CCA. Besides the improved survival rate (92% at 1 year, 82% at 3 years and 82% at 5 years), it resulted in better recurrence rates as well (0% at 1 year, 5% at 3 years and 12% at 5 years). Recently, another report from Mayo Clinic [48], involving 65 patients, showed a 5-year survival and disease-free survival rates of 76% and 60%, respectively. Same study reported on recurrence predictors which included high pretransplant CA19-9 levels, residual tumour in explant ≥2 cm, tumour grade, perineural invasion, cholecystectomy and advanced age. By using similar multimodality protocols for the treatment of patients with CCA comparable results have been achieved also by the group of Pittsburgh [49] and Omaha [50]. Sudan *et al.* [50], using a protocol of intense brachytherapy and 5-FU reached a 45% long-term survival at a median follow up of 7.5 years in 11 transplanted patients.

So far, current results from a number of studies show increased survival figures, in particular for well-selected patients with early tumour stages, suggesting that the OLT for early stage CCA is an effective treatment. Further improvements in long-term survival may be achieved with new adjuvant and neoadjuvant protocols. Patients with neoadjuvant radiochemotherapy show long-term results similar to those for liver transplantation for other indications. Also, photodynamic therapy and the use of new anti-proliferative immunosuppressive agents may be an approach for further improvement of the long-term results. However, the dilemma still remains as there is no clear consensus as to the optimum methods of evaluation and treatment of these difficult cases, particularly so when considering patients with well-localized tumours, who are also the patients likely to be amenable to conventional surgical treatment. Hence, the current strategy should emphasize that liver transplantation for the treatment of CCA should be restricted to centres with experience in the treatment of this cancer and should be taken into consideration in patients with contraindications to liver resection.

Epithelioid hemanigioendothelioma and angiosarcoma

Epithelioid hemangioendothelioma (EH) is a rare malignant tumour, originating from the vascular endothelium and predominantly affecting young female patients. The prognosis of this tumour is unpredictable and the morphological appearances do not correlate well with the biological behaviour. It is often misdiagnosed as metastatic disease, because of its multifocal nature. Although the potentially lengthy clinical course following diagnosis favours resection, partial hepatectomy is rarely feasible because of the multifocal liver involvement, making liver transplantation a more attractive option. Liver transplantation has been performed in patients and reported by a number of transplant units to have satisfactory results. Series from Pittsburgh [51] and Cincinnati Cancer Transplant Registry [39] have shown good results with a post-transplant 5-year and disease-free survival of 71–76% and 69–43% respectively. Similarly, a very recent series of 110 patients from ELTR [4] has shown a 1- and 5-year survival of 90% and 76%. Furthermore, a large multicentre review performed by Mehrabi *et al.* [52], revealed that among the used treatment modalities, liver transplant was the most efficacious, with a 1- and 5-year survival of 96% and 55%. In addition, liver resection was demonstrated as a nonsuitable treatment, because of the multifocal nature of the tumour as well as the fact that it triggers tumour growth, which is possibly related to the angiogenesis of the regenerating liver. On the other hand, based on the current available data, no clear definition about the impact of the nonsurgical treatments (radiotherapy, RFA, arterial embolization, chemoembolization) could be done, however, agents such as α-interferon, thalidomide and vincristine could play a role as neoadjuvant therapies to liver transplant.

Unlike the circumstances with other primary liver neoplasm, the presence of extrahepatic metastases does not correlate with survival, so this finding is not necessarily a contraindication to the liver transplant. For example, in the series reported by Marino *et al.* [53], five patients with metastases at the time of the transplantation were

alive at a mean of 41 months post-transplant. Same observation has been reported by the Heidelberg group [52] who had no deaths up to 151 months post-transplant in patients who were found to have metastases at the time of the transplantation. Lastly, a series from Lehrut [54] has shown no survival difference between transplanted patient with and without extrahepatic disease. Therefore, based on these reports, showing that long-term survival is possible even with the presence of extrahepatic metastases, selected patients with this tumour should be considered candidates for liver transplant.

Angiosarcoma is the main and very important differential diagnosis in suspected cases of EH. Angiosarcoma is a rapidly growing tumour with a very poor prognosis (median survival – 6 months) and has a male predominance. Death often occurs because of liver failure or severe haemorrhage secondary to tumour rupture. Bleeding is a particular presenting feature of the tumour because of its hypervascular nature as well as thrombocytopenia secondary to a consumption coagulopathy caused by the tumour. Regarding the treatment, in contrast to the good results of OLT for EH, transplantation for angiosarcoma is totally unsuitable yielding very poor results because of early tumour recurrence. Patients have been transplanted either on the basis of a presumed diagnosis of EH or as an intentional therapeutic strategy, however, most of them died within a year of transplantation, and no patients survived beyond 28 months [55]. Likewise, ELTR data analysis has revealed that 17 transplanted patients for angiosarcoma had a median survival of 7 months [56]. Therefore, transplantation is not indicated for patients with angiosarcoma. Likewise, no survivors have been reported after treatment by resection and/or chemotherapy.

Hepatoblastoma

Although primary liver tumours account for less than 2% of paediatric malignancies, hepatoblastoma (HB) is the most common hepatic malignancy of childhood, with the highest incidence in the first 3 years of life. During the 1980s, a dramatic improvement in the prognosis for HB was observed with the development of effective cisplatin-based chemotherapy regimens. Thus, the basis of the initial therapy is chemotherapy (cisplatin and doxorubicin) aiming to reduce the tumour burden. Despite the progress made, disease-free survival for HB depends on the resectability and complete surgical resection is essential for cure. Liver transplant as surgical therapy has become a recognized treatment for patients with unresectable disease limited to liver after chemotherapy. Additionally, liver transplant plays a role in cases of incomplete resection or tumour recurrence. Since late 1980s, a significant number of OLTs have been performed in paediatric patients for HB with good results. In a review of international experience published by Otte *et al.* [57] (Table 4), 106 recipients of a primary liver transplant showed significantly better overall survival of 82% at 6 years as compared to that of 30% of the 41 patients who received the transplant as a 'rescue procedure' performed after an incomplete resection or after intrahepatic recurrence following hepatectomy. Seven of the 12 transplanted patients who had pulmonary metastases at presentation survived. Another report from US [58], involving 135 children transplanted with HB between 1987 and 2004, showed an actuarial survival at 5 and 10 years of 69% and 66% respectively. Similar results are reported by other single-centre studies. For instance, a Japanese group [59] whose series included 14 patients reported a 72% overall survival, whereas, Pimpalwar *et al.* [60] reported a 100% survival for patients who responded to chemotherapy, followed by OLT. In contrast, a survival of 60% was seen in nonchemo responders who received OLT. Some evidence supporting the efficacy of liver transplantation comes from another series form the Paediatric Liver Center in Cincinnati [61] involving eight patients treated with transplant reporting a survival of 88% at 7 years (one death only). Also, the latest ELTR report, which includes 129 patients with HB, has shown a 1- and 5-year survival of 100% and 74% respectively.

Table 4. Liver transplantation results for hepatoblastoma (HB).

Author/Institution	Year	Patients	Overall survival (%)
Reyes *et al.*	1998	12	83
Pimpalwar *et al.*	2001	16	79
Srinivasan *et al.*	2001	10	100
Molmenti *et al.*	2001	11	66
Siopel – 1	2001	12	66
UNOS Report	2004	135	66
ELTR Report	2007	129	74

In conclusion, it is well established that the combination of chemotherapy and surgery is the accepted primary treatment for HB, however, liver transplant is recognized as a viable option and it should be considered for patients having either unresectable or recurrent primary hepatic malignancy, as it is the only treatment which can result in long-term survival.

Metastatic neuroendocrine tumours

Neuroendocrine (NE) tumours are slow-growing neoplasm, frequently presenting with multifocal and bilateral liver metastases. Metastases from NE tumours commonly present with a twin problem: tumour bulk and disabling

clinical syndromes secondary to their hypersecretory activity. The hormones produced usually are serotonin, insulin, gastrin, glucagon, etc, but also may present as a nonfunctioning mass lesion.

A number of treatments have been utilized for the management of these tumours, including chemotherapy (somatostatin analogues, streptozocin), interventional techniques (arterial embolization, chemoembolization, RFA), unfortunately they remain in a palliative context, producing poor survival rates (5-year survival 11–40%) [62]. Curative hepatic surgery although a very attractive alternative, is seldom possible as the hepatic metastases are multifocal and bilateral in 90% of the cases [63]. Nevertheless, palliative resections are believed to be beneficial if 80–90% of the tumour bulk can be removed, resulting in a considerable symptomatic improvement as well as in a 5-year survival of 50% [64].

Liver transplantation has been proposed as a treatment of unresectable or symptomatic tumours, which do not respond to the medical or interventional therapy. Lehnert [65] in a review of 103 patients transplanted for NE tumour metastases found that the 2- and 5-year survival rates were 60% and 47%. As per his report, survival seemed to be favourably influenced by age less than 50 years, type of the primary tumour, less extensive abdominal surgery and octreotide treatment prior to transplant. On the other hand, a multicentric French review by Le Treut *et al.* [66], identified upper abdominal exenteration, primary tumour located in duodenum and/or pancreas and hepatomegaly as poor prognostic factors, concluding that their presence is a contraindication to transplantation. In fact, the 5-year survival post-OLT of the patients with one or more of the identified factors was 12% as opposed to a 5-year survival of 68% observed among patients who did not have them. Other studies (Table 5) have reported post-OLT 5-year survival rates ranging between 33% and 80% [67], and a 5-year disease-free survival ranging between 17% and 24% [68].

Lang *et al.* [69], reported an actuarial survival of 75%, with a median follow up of 34 months. Fifty-eight percent of these patients developed recurrence, whereas, Florman *et al.* [70] reported 1- and 5-year survival post-OLT of 73% and 36% respectively. The experience of liver transplantation for patients with NE metastases indicates that transplantation should be done on a very selective basis. The current view [71] is that a better selection of patients, by examining the histological and cytological tumour features, by reducing the perioperative mortality possibly by doing staged resections, rather than doing complex resections at the time of the OLT, is a strategy that offers a number of advantages. Besides reducing the risk of the OLT, this approach allows a time period to observe the natural progression of the tumour. Other factors that have been used in selection of the patients for transplant are: proven absence of extrahepatic tumour over 6 months, and hormonal symptoms refractory to medical therapy. In addition, it has been suggested that tumour markers may play a role as prognostic factors. A recent study has demonstrated that low tumour expression of Ki67 (<5%) and E-cadherin may be associated with a better outcome following OLT for metastatic NE tumours [72]. Low levels of the Ki67, in well-differentiated NE tumours showed a better relief of the hormonal symptoms as well as disease-free survival. Similarly, MIB-1antibody has been shown to accurately assess the cell proliferation activity, which is useful in predicting post-transplant recurrence [73].

Table 5. Liver transplantation results for neuroendocrine (NE) tumours.

Author/Institution	Year	No. of patients	Patient survival (%)		
			1-year	3-year	5-year
Alessiani *et al.*	1995	14	64	64	64
Routley *et al.*	1995	11	82	57	28
Le Treut *et al.*	1997	31	58	47	36
Lang *et al.*	1997	12	82	82	82
Olausson *et al.*	2002	9	89	–	–
Rosenau *et al.*	2002	19	89	–	80
Florman *et al.*	2004	11	73	–	36
ELTR Report (Other NE tumours)	2007	120	81	65	53
ELTR Report (Carcinoid)	2007	159	88	–	52
Le Treut *et al.*	2007	85	–	–	68

In conclusion, different data would suggest that liver transplant should be considered in patients with no evidence of extrahepatic tumour and in whom all other therapeutic options are no longer effective. In selected group of patients, liver transplant is part of the therapeutic options for NE tumour metastases and may provide not only long-term symptomatic relief but also possible cure. Also, the emphasis is given to a better patient selection, development of new protocols as well as conducting more studies to evaluate selection new biological markers with a prognostic value.

Colorectal liver metastases

The feasibility of OLT for colorectal (CRC) liver metastases has been little explored as in general this condition is considered as an absolute contraindication to liver transplantation. Interestingly enough, until 1994, liver transplantation was an additional treatment option for patients whose tumour was unresectable. So far, 55 transplanted patients with CRC liver metastases have been

reported to ELTR [4]. Among these, the largest historical series came from a group in Vienna [74], which included 24 patients transplanted over a 10-year period (1983–1994). Based on the latest ELTR report, the 1- and 5-year survival is 62% and 18% respectively.

Although, the CRC liver metastases at the present are considered as a contraindication to transplantation, it is interesting to note that this policy is based entirely on the poor results obtained as far as 15 years ago, in a context of organ shortage. The analysis of the transplanted patients with CRC liver metastases has shown that 80% of these procedures were performed before 1995, a period characterized by lack of adequate selection strategies, standardized immunosuppression protocols and operative expertise (20 centres had performed <3 transplantations for this indication). Furthermore, the graft loss in 44% of patients was not related to tumoral recurrence. In addition, nine of the 50 transplanted patients survived at 5 years, two of which had no tumour recurrence as far as 9 and 21 years post-transplant.

Hence, a logical deduction would be that long-term survival and even of cure could potentially be possible for some patients. But is it justified to reconsider liver transplantation as a treatment option for CRC liver metastases in the current situation? The advances made in the field of transplantation as well as oncological treatment of the CRC metastases, certainly favour this consideration.

For example, the overall results of liver transplantation in Europe and elsewhere have dramatically improved with an actual 5-year survival of 71%, which is in a sharp contrast to the 5-year survival of 21% in mid 80s, or to the 5-year survival of 52% and 65% achieved between 1985 and 1989, also between 1990 and 1994 respectively. On the other hand, the combination of the newer chemotherapy agents with 'rescue liver surgery [75]' has resulted in achieving a 5-year survival of 30% for patients who not very long ago were considered to have a very poor prognosis. It is very likely that these results will continue to improve and this would unquestionably have an impact on the results of transplantation for CRC liver metastases.

Dramatic progress has also been made in the diagnostic imaging of the intra- and extra-hepatic metastases. The wide use of spiral CT scan and PET scan has certainly increased the rate of preoperative identification of metastases, often missed with conventional imaging modalities. This has resulted in a better patient selection and consequently in a better survival after liver surgery. Therefore, it is very likely that the same benefit could be obtained for transplant candidates. Excluding (based on accurate imaging) patients who in the past were considered as good candidates, and also selecting those who have only localized liver disease, would without doubts positively impact the post-transplant survival. Last, immunohistochemical markers (Kiras, P53) are other factors, which definitely can play an important role in the selection process by early identification and exclusion of patients with poor prognosis from the outset.

In conclusion, although, at the present time the OLT experience for CRC liver metastases remains limited, the observed good survival results, albeit in a small number of patients, would be an argument to consider re-exploration of this treatment alternative in an attempt to extend the benefits of OLT to a well selected group of patients (unresectable liver metastases, good responders to chemotherapy, disease limited to liver only). For the very few potential candidates selection is the key word, and there is no doubt that in the future, liver transplantation could play a role in the management CRC liver metastases; however, considering that OLT for this indication is at best an experimental procedure of unknown cost effectiveness, its application should strictly be done as part of a well-designed clinical trial.

References

1. Bismuth H, Chiche L, Adam R, Castaing D, Diamond T, Dennison A. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. *Ann Surg* 1993; **218**: 145.
2. 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.
3. United network for Organ Sharing. Policy 3.6. http://www.unos.org/data/about/viewDataReport.
4. European Liver Transplant Registy. *Data Analysis Booklet*. Paris: 2007: http://www.eltr.org.
5. Cillo U, Vitallo A, Bassanello M, *et al.* Liver transplantation for the treatment of moderately or well differentiated hepatocellular carcinoma. *Ann Surg* 2004; **239**: 150.
6. Yao FY, Ferrell L, Bass NM, *et al.* Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001; **33**: 1394.
7. Ravaioli M, Ercolani G, Cescon M, *et al.* Liver transplantation for hepatocellular carcinoma: further consideration on selection criteria. *Liver transpl* 2004; **10**: 1195.
8. Fernandez JA, Robles R, Marin C, *et al.* Can we expand the indications for liver transplantation among hepatocellular carcinoma patients with increased tumor size? *Transplant Proc* 2003; **35**: 1818.
9. Yao FY, Xiao L, Bas NM, Kerlan R, Ascher NL, Robert JP. Liver transplantation for hepatocellular carcinoma: validation of UCSF criteria based on preoperative imaging. *Am J Transplant* 2007; **7**: 2587.

10. Sotiropoulops G, Malago M, Molmenti E, *et al.* Liver transplantation for hepatocellular carcinoma in cirrhosis. Is clinical tumor classification before transplantation realistic? *Transplantation* 2005; **79**: 483.
11. Duffy JP, Vardanian A, Benjamin E, *et al.* Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22 year experience with 467 patients at UCLA. *Ann Surg* 2007; **246**: 502.
12. Schwartz M. Liver transplantation for hepatocellular carcinoma. *Gastroenterology* 2004; **127**: 268.
13. Leung JY, Zhu AX, Gordon FD, *et al.* Liver transplantation outcomes for early stage hepatocellular carcinoma: results of a multicenter study. *Liver Transpl* 2004; **10**: 1343.
14. Marsh JW, Dvorchik I. Liver organ allocation for hepatocellular carcinoma. Are we sure?. *Liver Transpl* 2003; **9**: 693.
15. Decaens T, Roudot-Thoraval F, Bresson-Hadni S, *et al.* Impact of UCSF criteria according according to pre and post OLT tumor features: analysis of 479 patients listed for HCC with a short waiting time. *Liver Transpl* 2006; **12**: 1761.
16. Adam R, Del Gaudio M. Evolution of liver transpnatation for hepatocellular carcinoma. *Journal Hepatol* 2003; **39**: 888.
17. Bruix J, Fuster J, Llowet JM. Liver transplantation for hepatocellular carcinoma: Foucoult Pendulum versus evidence based decision. *Liver Transpl* 2003; **7**: 700.
18. Yao FY, Ferrel L, Bass NM, *et al.* 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.
19. Llowet JM, Fuster J, Bruix J. Intention to treat analysis of surgical treatment for early hepatocellular carcinoma: Resection versus transplantation. *Hepatology* 1999; **30**: 1434.
20. Yao FY, Bass NM, Nicolai B, *et al.* Liver transplantation for hepatocellular carcinoma: analysis of survival according to intention to treat principle and drop out from the waiting list. *Liver Transpl* 2002; **8**: 873.
21. Sarasin FP, Majno PE, Llovet JM, Bruix J, Mentha G, Hadengue A. Living donor liver transplantation for early hepatocarcinoma: a life expectancy and cost effectiveness perspective. *Hepatology* 2001; **33**: 1073.
22. Todo S, Furukawa H. Japanese Study Group on Organ Transplantation. Living donor liver transplantation for adult patients with hepatocellular carcinoma. Experience in Japan. *Ann Surg* 2004; **240**: 451.
23. Trotter JF, Wisniewski K, Terrault N, *et al.* Outcomes of donor evaluation in adult to adult living donor transplantation. *Hepatology* 2007; **46**: 1476.
24. Trotter JF, Adam R, Lo CM, Kenison J. Documented deaths of hepatic lobe donors for living donor liver transplantation. *Liver Transpl* 2006; **12**: 1485.
25. Middleton PF, Duffield M, Lynch SV, *et al.* Living donor liver transplantation – adult donor outcomes: a systematic review. *Liver Transpl* 2006; **12**: 24.
26. Bigourdan JM, Jaeck D, Meyer N, *et al.* Small hepatocellular carcinoma in Child A cirrhotic patients: hepatic resection versus transplantation. *Liver Transpl* 2003; **9**: 513.
27. Toso C, Meeberg GA, Bigam DL, *et al.* de novo Sirolimus based immunosuppression after liver transplantation for hepatocellular carcinoma: long term outcomes and side effects. *Transplantation* 2007; **83**: 1162.
28. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Long term survival and patern of recurrence after resection of small hepatocellular carcinoma in patients with preserved liver function: implications for a strategy of salvage transplantation. *Ann Surg* 2002; **3**: 373.
29. Mazzaferro V, Battiston C, Perrone S, *et al.* Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. *Ann Surg* 2004; **240**: 900.
30. Briyet PY, Paradis V, Brancatelli G, *et al.* Percutaneous radiofrequency ablation for hepatocellular carcinoma before liver transplantation: a prospective study with histopathologic comparison. *AJR Am J Roentgen* 2006; **186**: S296.
31. Fontana RJ, Hamidullah H, Nghiem H, *et al.* Percutaneous radiofrequency thermal ablation of hepatocellular carcinoma: a safe and effective bridge to liver transplantation. *Liver transplantation* 2002; **8**: 1165.
32. Adam R, Azoulay D, Castaign D, *et al.* Liver resection as a bridge to transplantation for hepatocellular carcinoma on cirrhosis. *Ann Surg* 2003; **238**: 508.
33. Belghiti J, Cortes A, Abdalla EK, *et al.* Resection prior to liver transplantation for hepatocellular carcinoma. *Ann Surg* 2003; **238**: 885.
34. Hwang SH, Lee SG, Moon DB, *et al.* Salvage living donor liver transplantation after prior liver resection for hepatocellular carcinoma. *Liver Transpl* 2007; **13**: 741.
35. Khan SA, Thomas HC, Davidson BR, Taylor Robinson SD. Cholangiocarcinoma. *Lancet* 2005; **366**: 1303.
36. Khan SA, Davidson BR, Goldin R, *et al.* Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. *Gut* 2002; **51**: vi1.
37. Klintmalm GB, Stone MJ. Liver transplantation for malignancy. *Transplant Rev* 1990; **4**: 52.
38. Iwatsuki S, Gordon RD, Shaw Jr BW, Starz TE. Role of liver transplantation in cancer therapy. *Ann Surg* 1985; **202**: 401.
39. Penn I. Hepatic transplantation for primary and metastatic cancers of the liver. *Surgery* 1991; **110**: 726.
40. Ringe B, Wittekind C, Bechstein WO, *et al.* The role of liver transplantation in hepatobiliary malignancy. *Ann Surg* 1989; **209**: 88.
41. Robles R, Figueras J, Turrion VS, *et al.* Spanish experience in liver transplantation for hilar and peripheral cholangiocarcinoma. *Ann Surg* 2003; **239**: 265.
42. Robles R, Figueras J, Turrion VS, *et al.* Liver transplantation for hilar cholangiocarcinoma Spanish experience. *Transplant Proc* 2003; **35**: 1821.
43. Figueras J, Llado L, Valls C, *et al.* Changing strategies in diagnosis and management of hilar cholangiocarcinoma. *Liver Transpl* 2000; **6**: 786.
44. Senzer NN, Stone MJ, Klintmalm GB, *et al.* Adjuvant radiochemotherapy following orthotopic liver

transplantation for bile duct cancer. *Transplantation* 1990; **50**: 1045.
45. Klemnauer J, Ridder GJ, Werner M, Weimann A, Pichlmayr R. What constitutes long term survival after surgery for hilar cholangiocarcinoma? *Cancer* 1997; **79**: 26.
46. Foo ML, Gunderson LL, Bender CE, Buskirk SJ. External radiation therapy and transcatheter iridium in the treatment of the extrahepatic bile duct carcinoma. *Int J Radiat Oncol Biol Phys* 1997; **39**: 929.
47. De Vreede I, Steers JL, Burch PA, *et al.* Prolonged disease free survival after orthotopic liver transplant plus adjuvant chemoirradiation for cholangiocarcinoma. *Liver Transpl* 2000; **6**: 309.
48. Heimbach JK, Gores GJ, Haddock MG, Albert SR, *et al.* Predictors of disease recurrence following neoadjuvant chemoradiotherapy an liver resection for unresectable perihilar cholangiocarcinoma. *Transplantation* 2006; **82**: 1703.
49. Urego M, Flickinger JC, Carr BI. Radiotherapy and multimodality management of cholangiocarcinoma. *Int J Radiat Oncol Biol Phys* 1999; **44**: 121.
50. Sudan D, De Roover A, Chinnakotla S, *et al.* Radiochemotherapy and transplantation allows long term survival for non resectable hilar cholangiocarcinoma. *Am J Transplant* 2002; **2**: 774.
51. Madariaga JR, Marino IR, Karavias DD, *et al.* Long term results after liver transplantation for primary hepatic epithelioid hemangioendothelioma. *Ann Surg Oncol* 1995; **2**: 483.
52. Mehrabi A, Kashfi A, Schemmer P, *et al.* Surgical treatment of primary epithelioid hemangioepithelioma. *Transplantation* 2005; **80**: 109.
53. Marino IR, Todo S, Tzakis IG, *et al.* Treatment of hepatic epithelioid hemangioepithelioma with liver transplantation. *Cancer* 1988; **62**: 2079.
54. Lerut J, Orlando G, Adam R, *et al.* The place of liver transplantation in the treatment of hepatic epithelioid hemangioendothelioma. Report of the European liver transplant registry. *Ann Surg* 2007; **246**: 949.
55. Selzner M, Clavien PA. Liver tumors of rare and unknown origins. In: Clavien PE, ed. *Malignant Liver Tumors*. Malden: Blackwell Science, 1999: 303–312.
56. Lehrut J. Liver transplantation and vascular tumors. *7th World Congress of the International Hepato-Pancreato-Biliary Association in Edinburgh UK*, 2006.
57. Otte JB, Pritchard J, Aronson DC, *et al.* Liver transplantation for hepatoblastoma: results from the International Society of Pediatric Oncology (SIOP) Study SIOPEL – 1 and review of the world experience. *Pediatr Blood cancer* 2004; **42**: 74.
58. Austin MT, Leys CM, Feurer ID, *et al.* Liver transplantation for childhood hepatic malignancy: a review of the UNOS data base. *J Pediatr Surg* 2006; **41**: 182.
59. Kasahara M, Ueda M, Haga H, *et al.* Living donor liver transplantation for hepatoblastoma. *Am J Transplant* 2005; **5**: 2229.
60. Pimpalwar AP, Sharif K, Ramani P, *et al.* Strategy for hepatoblastoma management: transplant versus nontransplant surgery. *J Pediatr Surg* 2002; **37**: 240.
61. Tiao GM, Bobey N, Allen S, *et al.* The current management of hepatoblastoma: a combination of chemotherapy, conventional resection, and liver transplantation. *J Pediatr* 2005; **146**: 204.
62. Soreide O, Berstad T, Bakka A, *et al.* Surgical treatment as a principle in patients with advanced abdominal carcinoid tumors. *Surgery* 1992; **111**: 726.
63. Ihse I, Persson B, Tibblin S. Neuroendocrine metastases of the liver. *World J Surg* 1995; **19**: 76.
64. Carty SE, Jensen RT, Norton JA. Prospective study of aggressive resection of metastatic pancreatic endocrine tumors. *Surgery* 1992; **112**: 1024.
65. Lehnert T. Liver transplantation for metastatic neuroendocrine carcinoma: an analysis of 103 patients. *Transplantation* 1998; **66**: 1307.
66. Le Treut YP, Grégoire E, Belghiti J, *et al.* Location of the primary tumor and liver size are predictors for survival after liver transplantation for endocrine metastases. An 85-case French multicentric series. *Liver Transplant* 2007; **13**: S 159.
67. Le Treut YP, Delpero JR, Dousset B, *et al.* Results of liver transplantation in the treatment of metastatic neuroendocrine tumors. A 31-case French multicentric report. *Ann Surg* 1997; **225**: 355.
68. Ahlman H, Friman S, Cahlin C, *et al.* Liver transplantation for treatment of metastatic neuroendocrine tumoes. *Ann NY Acad Sci* 2004; **265**: 1014.
69. Lang H, Oldhafer KJ, Weimann A, *et al.* Liver transplantation for metastatic neuroendocrine tumors. *Ann Surg* 1997; **225**: 347.
70. Florman S, Toure B, Kim L, *et al.* Liver transplantation for neuroendocrine tumors. *J Gastrointest Surg* 2004; **8**: 208.
71. Sutcliffe R, Maguire D, Ramage J, *et al.* Management of neuroendocrine liver metastases. *Am J Surg* 2004; **187**: 39.
72. Rosenau J, Bahr MJ, Von Wasielewski R, *et al.* Ki67, e-cadherin, and p53 as prognostic indicators of long term outcome after liver transplantation for metastatic neuroendocrine tumors. *Transplantation* 2002; **73**: 386.
73. Amarapurkar AD, Davies A, Ramage JK, Stangou AJ, Wight DG, Portman BC. Ploriferation of antigen MIB-1 in metastatic carcinoid tumors removed at liver transplantation: revelance to prognosis. *Eur J Gastroenterol Hepatol* 2003; **15**: 139.
74. Muhlbacher F, Huk I, Steininger R, *et al.* Is orthotopic liver transplantation a feasible treatment for secondary cancer of the liver? *Transplant Proc* 1991; **23**: 1567.
75. Adam R, Delvart V, Pascal G, *et al.* Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: A model to predict long term survival. *Ann Surg* 2004; **240**: 644.

