Transplant International

Transplant International ISSN 0934-0874

REVIEW

Liver transplantation for unresectable hepatocellular carcinoma in patients without liver cirrhosis

Hynek Mergental[1] and Robert J. Porte[2]

1 Oxford Transplant Centre and Department of Hepato-Pancreato-Biliary Surgery, Oxford Radcliffe Hospitals NHS Trust, Churchill Hospital, Oxford, UK

2 Department of Hepato-Pancreato-Biliary Surgery and Liver Transplantation, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

Keywords
hepatocellular carcinoma, liver resection, liver transplantation, noncirrhotic, recurrent, unresectable.

Correspondence
Robert J. Porte MD, PhD, Department of Hepato-Pancreato-Biliary Surgery and Liver Transplantation, University Medical Center Groningen, PO Box 30.001, 9700 RB Groningen, The Netherlands. Tel.: +31 50 361 2896; fax: +31 50 361 1745; e-mail: r.j.porte@chir.umcg.nl

Received: 30 November 2009
Revision requested: 17 January 2010
Accepted: 17 February 2010
Published online: 12 March 2010

doi:10.1111/j.1432-2277.2010.01076.x

Summary

Hepatocellular carcinoma (HCC) arising in noncirrhotic and nonfibrotic liver (NC-HCC) is a rare type of malignancy frequently found in healthy young individuals. Partial liver resection is the treatment of choice with expected 5-year survival rates between 40% and 70%. As a result of absence of any symptom, a considerable number of patients are diagnosed when the malignancy has progressed to an advanced stage and the tumor has turned already unresectable. Some other patients suffer from intrahepatic recurrence after previous liver resection that cannot be re-resected or locally ablated. In these situations, liver transplantation (LT) may be the only potentially curative treatment. The indication for LT in NC-HCC patients, however, is not well established. The preliminary results of recent analysis of the European Liver Transplant Registry (ELTR) together with a literature review identified over 150 patients transplanted for NC-HCC during the last 15 years. In contrast to the historical data, these studies showed 5-year survival rates at 50–70% in well-selected patients. Important determinants of poor outcome are macrovascular invasion, lymph node involvement, and time interval of <12 months when LT is used as rescue therapy for intrahepatic recurrence after a previous partial liver resection. Interestingly, outcomes after both liver resection and LT for NC-HCC are much less influenced by tumor size than is the case with cirrhotic HCC. A large tumor size *per se* should, therefore, not to be seen as a strict contraindication for performing LT in patients with NC-HCC.

Introduction

Hepatocellular carcinoma (HCC) arising in a noncirrhotic and nonfibrotic liver (NC-HCC) is a rare type of malignancy. It is estimated that only 5–15% of all HCC arise in an otherwise normal liver [1–3]. In contrast to the more common type of HCC which can be found in cirrhotic livers, NC-HCC is frequently found in otherwise healthy and young individuals. The peak incidence of NC-HCC is in the fourth decade, as compared with an age peak in fifth and sixth decade for HCC in diseased livers [4]. In contrast to patients with HCC in a cirrhotic or fibrotic liver, NC-HCC typically occurs in patients without chronic hepatitis B or C infection and without any other apparent chronic inflammation of the liver. The etiology of NC-HCC is largely unknown, although some investigators have suggested a link with the long-term use of estrogens. While HCC in cirrhotic livers is predominantly found in male patients, NC-HCC is found more frequently in female patients. In the absence of a symptomatic underlying disease, the diagnosis of NC-HCC is usually made at advanced stage when patients have already developed large tumors.

Partial liver resection is the treatment of choice for NC-HCC [3,5–7]. However, a considerable number of patients are diagnosed at an advanced stage when the tumor is already unresectable, either because of tumor size, anatomical localization, or the presence of multiple bilobar intrahepatic metastases. The mean tumor size in most published series of patients undergoing partial liver resection for NC-HCC exceeds 10 cm [8–11]. In addition to patients presenting with a large primary NC-HCC, there is a second group of patients who suffer from intrahepatic recurrence after previous partial liver resection that cannot be removed by repeated liver resection or a local ablative technique. In these situations, liver transplantation (LT) may be the only potentially curative treatment option.

The indication for LT in patients with NC-HCC, however, is not well established. As a result of the late symptoms in otherwise healthy patients, tumor size and number of nodules at the time of presentation may be outside the widely accepted international (Milan) criteria for LT as treatment for HCC in cirrhotic livers [12]. On the other hand, it is likely that the Milan criteria and the algorithms used for HCC in cirrhotic livers are not applicable to NC-HCC, as it is a different disease with probably a different etiology and pathogenesis [13].

History

In the early era of LT, many patients with HCC were transplanted for unresectable liver tumors. However, at that time extension of tumor to adjacent organs, and macrovascular or lymph node involvement were not yet recognized as risk factors of very poor outcome after LT. As patients without underlying liver disease were transplanted in general in more advanced stages as compared with cirrhotic patients, the outcome was worse, and the absence of liver cirrhosis has later been identified as a risk factor for a very poor prognosis [4,14]. In 1999, Houben and McCall reported an overview of 126 patients who had been transplanted for NC-HCC and whose cases were reported in the literature between 1966 and March 1998 [15]. The observed outcome was poor and although results were better in patients who underwent transplantation for fibrolamellar NC-HCC than for nonfibrolamellar NC-HCC (5-year survival rates of 39.4% and 11.2% respectively), LT for NC-HCC was in general discouraged. Unfortunately, despite the relatively large number of patients in that review, there was insufficient information available to determine the influence of tumor characteristics, such as tumor size, tumor distribution, stage, and vascular invasion, on outcome after LT.

Partial liver resection

Contrary to disappointing results after LT, several studies have shown better outcomes when patients with NC-HCC were treated by partial liver resection. Ringe *et al.* reported a 5-year survival rate after partial liver resection of 45% compared to 12% for patient being transplanted [4]. This historical study, as well as several other series reported thereafter, strongly indicated that partial liver resection is the treatment of choice for noncirrhotic patients whenever this is technically feasible. Although selection bias may well explain the differences in outcome after partial liver resection and LT for NC-HCC, it is conceivable that immunosuppressive therapy needed after LT may also play a role as it may facilitate outgrowth of micrometastases as a result of a reduced anti-cancer immune surveillance.

Over the past 15 years the reported results after partial liver resection for NC-HCC have steadily improved (Table 1). Several investigators have tried to identify variables that are associated with poor outcome. These variables include the presence of vascular invasion, multiple tumors, absence of tumor capsule, lymph node involvement and perioperative administration of blood transfusion. [6,8,16–18]. Interestingly, several reports have suggested that outcome after partial liver resection for NC-HCC is not influenced by tumor size [10,16,17]. Most recent series have indicated that partial liver resection for NC-HCC may result in 5-year survival rates varying between 40% and 70% and 5-year tumor-free survival rates varying between 30% and 50% [6,8,10,16–24]. The prognosis for unresectable NC-HCC, however, is rather poor with an expected median survival time of about 30–40 weeks and a 5-year survival rate <3% [25,26].

Liver transplantation

In the early 1990s several groups have reported excellent results in patients transplanted for early stages of HCC in cirrhotic livers and this has started the modern era of LT for HCC. The so called Milan criteria were widely adopted (one nodule of HCC ≤5 cm or ≤3 nodules each ≤3 cm) as the accepted indication criteria for LT in patients with HCC [12]. This, however, resulted in the acceptance of only very few patients with NC-HCC for LT as virtually all patients with NC-HCC have a late presentation and tumor diameter and numbers that exceed the limits of the Milan criteria. Indeed, in most recent years LT was mainly considered in patients with intrahepatic recurrences of NC-HCC after a previous partial liver resection. These patients are usually in a close follow-up schedule and recurrence is generally detected earlier in this situation. In a recent analysis of the European

Table 1. Overview of articles published between 1995 and 2009 reporting patients with noncirrhotic HCC treated by liver resection.

Author (study period)	Year [reference]	HCC variant number of pts	1-year survival (%)	5-year survival (%)	1-year TFS (%)	5-year TFS (%)	Risk factors for tumor recurrence	Summary
Rayya (2001–2006)	2008 [19]	NC-HCC 54	69	48	–	–	Not reported	38 cases noncirrhotic and nonfibrotic liver, 16 patients with fibrotic livers
Lubrano (1985–2005)	2008 [20]	NC-HCC 20	85	64	84	58	Cytolysis following TACE, R0 resection (factors associated with better results)	Mean tumor size 9.0 cm, 45% positive VI, 40% positive LN, 75% R0 resection, median time to recurrence 15 months, 5-year survival for patients with recurrence 25%
Bege (1987–2005)	2007 [8]	NC-HCC 116	72	40	–	–	Vascular invasion, multiple tumors, high AFP, R1/R2 resection	Mean tumor size 10.6 cm, 48% positive VI, 15% macrovascular VI, 90% R0 resection, 77% patients without fibrosis, 30% pts positive viral hepatitis serology (HBV/HCV), median follow-up 79 months
Lang (1998–2005)	2007 [21]	NC-HCC 83	77	30	–	–	Vascular invasion, R1/R2 resection, UICC tumor stage, tumor grading	Mean tumor size 9.0 cm, 54% positive VI, 12% macrovascular VI, 4% positive LN, 66% single tumor nodule, 76% R0 resection, 22% pts positive viral hepatitis serology (HBV/HCV), median follow-up 25 months
Capussotti (1985–2002)	2006 [22]	NC-HCC 47	–	31	–	34	Tumor size >10 cm, multiple (satellite) tumors	–
Laurent (1985–2002)	2005 [17]	NC-HCC 108	–	43	–	29	Multiple tumors, absence of tumor capsule, perioperatively RBC transfusions, resection margin <1 cm	Mean tumor size 9.3 cm, 53% positive VI, 25% macrovascular VI, 85% R0 resection, median follow-up 23 month
Dupot-Bierre (1998–2003)	2005 [16]	NC-HCC 84	78	44	–	–	Multiple tumors, macroscopic VI, non use of preoperative iodine-131 lipiodol infusion	Mean tumor size 8.6 cm, 45% positive VI, 11% macrovascular VI, 83% R0 resection, 7% pts positive viral hepatitis serology (HBV/HCV), median follow-up 25 months
Eguchi (1980–2003)	2005 [23]	NC-HCC 27	89	67	62	28	–	Mean tumor size 9.0 cm, 44% positive VI, median follow-up 35 months, included only noncirrhotic, nonfibrotic patients without viral hepatitis
Verhoef (1987–2000)	2004 [10]	NC-HCC 22	96	68	86	56	Vascular invasion, portal vein thrombosis, positive LN	Mean tumor size 10.0 cm, 82% single tumor nodule, 5% positive LN, 100% R0 resection, 32% pts positive viral hepatitis serology (HBV/HCV), minimum follow-up 37 months
Grazi (1981–2002)	2003 [18]	NC-HCC 135	84	51	78	46	Multiple (satellite) tumors, age <60 years, macrovascular VI, perioperative RBC transfusions	Mean tumor size 7.9 cm, 53% positive VI, 8% macrovascular VI, 87% single tumor nodule, 35% pts positive viral hepatitis serology, median follow-up 28 months
Fong (1991–1998)	1999 [24]	NC-HCC 54	83	42	–	–	Vascular invasion, R1/R2 resection	54 patients out of 126 noncirrhotic patients underwent a liver resection, mean tumor size 10.0 cm, impossible to separate risk factors and other data for cirrhotic versus noncirrhotic patients
Bismuth (1970–1992)	1995 [6]	NC-HCC 68	74	40	69	33	Tumor size >9 cm, absence of tumor capsule	Mean tumor size 8.8 cm, 9% positive macrovascular VI, 9% pts positive viral hepatitis serology (HBV)

Table includes only NC-HCC series that majority of included patients did not have an underlying liver disease or viral hepatitis and only the most recent/complete report from each center.
pts, patients; TSF, tumor-free survival; VI, vascular invasion; LN, lymph node; HBV, hepatitis B virus; HCV, hepatitis C virus; TACE, transarterial chemoembolization; RBC, red blood cells; UICC, Union Internationale Contre le Cancer; R0, resection when tumor was completely removed; R1, resection with microscopic residual tumor left; R2, resection with macroscopic residual tumor left.

Table 2. Overview of articles published between 1995 and 2008 reporting patients with noncirrhotic HCC treated by liver transplantation.

Author (study period)	Year [reference]	HCC variant number of pts	1-year survival (%)	5-year survival (%)	Tumor-free rate (%)	Follow-up (months)	Article characteristics	Summary
Slater (2003–2004)	2004 [34]	FL-HCC 1	Yes	NA	No recurrence	12	Case report	Primary LDLT for FL-HCC, encasement of IVC; data about patient and tumor characteristics given
Margarit (1988–2000)	2002 [32]	FL-HCC 1	Yes	No	Died from recurrence	24	Case report	Pt with advanced FL-HCC, tumor infiltrated whole liver as well adjacent organs and lymph nodes; LT was combined with Whipple procedure, pt received right split graft; pulmonary recurrence 12 months after LT, pt died 24 months after LT
El-Gazzaz (1985–1998)	2000 [30]	FL-HCC 9	90	50	56	Median 35	Retrospective study	Reported 9 pts with unresectable FL-HCC treated by primary LT; detailed data about each patient and tumor given
Hemming (1982–1995)	1997 [28]	FL-HCC 1	Yes	Yes	Developed recurrence	>72	Case report	Pt received rescue LT for FL-HCC recurrence 6 years after liver resection; 6 years after LT extrahepatic recurrence for which performed liver and distal stomach resection; 13 years after LT alive without recurrence
Pinna (1968–1995)	1997 [29]	FL-HCC 9	100	30	20	Median 58	Retrospective study	Reported 41 patients with FL-HCC, LT group included 13 pts, 3 pts had cirrhosis and one of those reLT); 9 pts suitable for analysis, detailed data about each patient and tumor given; 3 pts standard LT, 6 pts LT combined with resection of adjacent organ as a result of an extrahepatic FL-HCC spreading (diaphragm/adrenal gland/pylorus + omentum/pancreas)
Pichlmayr (1972–1994)	1995 [7]	FL-HCC 8*	73	49	62	Median 36	Retrospective study	Reported 198 cases transplanted for liver malignancies, 8 for FL-HCC and 28 for NC-HCC; for the FL-HCC subgroup given data about survival, tumor stage and recurrence rate but no particular pt details given
Malago (1998–2003)	2006 [35]	NC-HCC 4	75	NA	No recurrence	Median 33	Retrospective study	Reported 34 pts with HCC treated by LT, 4 pts had recurrent NC-HCC, 2 pts within Milan criteria, 2 pts beyond (1 of those early postoperative death); impossible to identify particular patient details; all patients received LDLT
Hess (2000–2002)	2002 [33]	NC-HCC 1	Yes	NA	No recurrence	15	Case report	Pt underwent liver resection of 18 cm large NC-HCC. 6 months later re-resection of intrahepatic recurrence, 3 months after re-resection rescue LDLT, pt 15 months following LT alive without tumor; histological evaluation of explanted liver remnant did not reveal any tumor
Jonas (1989–2001)	2001 [31]	NC-HCC 1	Yes	Yes	Developed recurrence	146	Case report	Pt received rescue LT after 3× liver resection for NC-HCC, developed pulmonary tumor recurrence that was treated by lung resection 4 and 8 years post LT, 12 years after LT alive without recurrence
Figueras (1990–1998)	1999 [37]	NC-HCC 5*	80	60	80	–	Retrospective study	5 cases reported, 3 pts treated with primary LT, 2 pts rescue LT for intrahepatic recurrence, 3 pts were alive up to 89 months following LT, 1 pt developed recurrence 30 months after LT and 1 pt died early after LT because of ischemic graft failure; no pts details given
Schlitt (1972–1994)	1999 [14]	NC-HCC 25*	57	27	–	Median 36	Retrospective study	Study focused on pattern of HCC recurrence after LT for HCC in 69 pts; given only recurrence rate and overall survival, no data available for the NC-HCC subgroup; no pts details given

*Patients/articles not listing detailed patient data.

pt, patient; HCC, hepatocellular carcinoma; NC-HCC, nonfibrolamellar variant of noncirrhotic HCC; FL-HCC, fibrolamellar variant of noncirrhotic HCC; LT, liver transplantation; LDLT, living donor liver transplantation; reLT, liver retransplantation.

Liver Transplant Registry (ELTR), 44 patients where identified who underwent LT for intrahepatic recurrence of NC-HCC. The median tumor size in this cohort was 3.5 cm. However, many patients presented with multiple tumor nodules and only 25% fulfilled the Milan criteria [27].

We have recently reviewed the literature published over the last 15 years, identifying only 27 patients transplanted for NC-HCC (Table 2) [28–35]. In addition, a preliminary analysis of the ELTR has revealed a total of 108 patients that were transplanted for unresectable NC-HCC across Europe between 1995 and 2005 [11,27]. On combining the results of these two analyses, including a total of more than 150 patients, the 5-year patient survival rate after LT for NC-HCC appears to be around 50% for the whole patient population and up to 70% for patients without risk factors such as vascular or lymph node involvement, or multiple tumors.

Many of the patients reported in the literature as well as in the ELTR had very large tumors, exceeding the Milan criteria. For example, in the ELTR study the median tumor size was 8 cm [11,27]. Interestingly, in the overall analysis, tumor diameter was not identified as an independent determinant of survival after LT. This finding is in line with data obtained after partial liver resections, as described above. Variables that are associated with reduced survival after LT for NC-HCC include macrovascular invasion and positive hilar lymph node metastases. In addition, in patients transplanted for recurrent NC-HCC after a previous partial liver resection, a time period between the initial liver resection and LT of <12 months has been identified as a significant risk factor for poor outcome [11,27].

Summary

Partial liver resection is the treatment of choice in patients with HCC occurring in the absence of an underlying chronic liver disease. The results of LT for unresectable HCC in noncirrhotic livers have improved considerably over the last 15 years as a result of better patient selection, as well as better perioperative management and surgical care [36]. Most recent evidence suggests that 5-year survival rates of 50–70% can be obtained in selected patients, making LT as a treatment option worth considering for unresectable NC-HCC, especially because many of these patients are young and otherwise healthy individuals. In patients with NC-HCC, the results after LT seem to be less influenced by tumor size, especially when LT is used as primary therapy. Preliminary data from the ELTR study suggest that the Milan criteria are not applicable in the context of patients with NC-HCC.

Based on the recent evidence, we propose the following treatment strategy for patients with unresectable NC-HCC. Patients presenting with extrahepatic spreading or gross vascular involvement should be strictly refused for LT. Sampling of hilar lymph nodes at the beginning of the transplantation procedure should be seriously considered, as lymph node involvement is a strong negative predictor of outcome, especially in patients who have already proven vascular invasion, a high tumor recurrence rate can be expected when both risk factors are present. In addition, the presence of more than four tumor nodules and intrahepatic tumor recurrence within 12 months after initial partial liver resection should be considered as predictors of a poor outcome after LT. A large tumor size *per se* (outside the Milan criteria) should not be seen as a strict contraindication for considering LT in patients with NC-HCC.

Funding

No financial support has been received for this work. The authors have no potential conflicts of interest to disclose.

References

1. Bruix J, Sherman M, Llovet JM, *et al.* Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. *J Hepatol* 2001; **35**: 421.
2. Bosch FX, Ribes J, Borras J. Epidemiology of primary liver cancer. *Semin Liver Dis* 1999; **19**: 271.
3. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; **362**: 1907.
4. Ringe B, Pichlmayr R, Wittekind C, Tusch G. Surgical treatment of hepatocellular carcinoma: experience with liver resection and transplantation in 198 patients. *World J Surg* 1991; **15**: 270.
5. Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. *Semin Liver Dis* 2005; **25**: 181.
6. Bismuth H, Chiche L, Castaing D. Surgical treatment of hepatocellular carcinomas in noncirrhotic liver: experience with 68 liver resections. *World J Surg* 1995; **19**: 35.
7. Pichlmayr R, Weimann A, Oldhafer KJ, *et al.* Role of liver transplantation in the treatment of unresectable liver cancer. *World J Surg* 1995; **19**: 807.
8. Bege T, Le Treut YP, Hardwigsen J, *et al.* Prognostic factors after resection for hepatocellular carcinoma in nonfibrotic or moderately fibrotic liver. A 116-case European series. *J Gastrointest Surg* 2007; **11**: 619.
9. Le Treut YP, Pons J, Hardwigsen J, *et al.* [Hepatocellular carcinoma in a non-cirrhotic liver. Presentation of series of 77 operated patients]. *Chirurgie* 1999; **124**: 485.

10. Verhoef C, de Man RA, Zondervan PE, Eijkemans MJ, Tilanus HW, Ijzermans JN. Good outcomes after resection of large hepatocellular carcinoma in the non-cirrhotic liver. *Dig Surg* 2004; **21**: 380.
11. Mergental H, Adam R, Klempnauer JL, *et al.* Liver transplantation for hepatocellular carcinoma in non-cirrhotic livers. *Liver Transpl* 2007; **13**(Suppl. 1): S119. (abstract #197).
12. 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.
13. Wong N, Lai P, Lee SW, *et al.* Assessment of genetic changes in hepatocellular carcinoma by comparative genomic hybridization analysis: relationship to disease stage, tumor size, and cirrhosis. *Am J Pathol* 1999; **154**: 37.
14. Schlitt HJ, Neipp M, Weimann A, *et al.* Recurrence patterns of hepatocellular and fibrolamellar carcinoma after liver transplantation. *J Clin Oncol* 1999; **17**: 324.
15. Houben KW, McCall JL. Liver transplantation for hepatocellular carcinoma in patients without underlying liver disease: a systematic review. *Liver Transpl Surg* 1999; **5**: 91.
16. Dupont-Bierre E, Compagnon P, Raoul JL, Fayet G, de Lajarte-Thirouard AS, Boudjema K. Resection of hepatocellular carcinoma in noncirrhotic liver: analysis of risk factors for survival. *J Am Coll Surg* 2005; **201**: 663.
17. Laurent C, Blanc JF, Nobili S, *et al.* Prognostic factors and longterm survival after hepatic resection for hepatocellular carcinoma originating from noncirrhotic liver. *J Am Coll Surg* 2005; **201**: 656.
18. Grazi GL, Cescon M, Ravaioli M, *et al.* Liver resection for hepatocellular carcinoma in cirrhotics and noncirrhotics. Evaluation of clinicopathologic features and comparison of risk factors for long-term survival and tumour recurrence in a single centre. *Aliment Pharmacol Ther* 2003; **17**(Suppl. 2): 119.
19. Rayya F, Harms J, Bartels M, Uhlmann D, Hauss J, Fangmann J. Results of resection and transplantation for hepatocellular carcinoma in cirrhosis and noncirrhosis. *Transplant Proc* 2008; **40**: 933.
20. Lubrano J, Huet E, Tsilividis B, *et al.* Long-term outcome of liver resection for hepatocellular carcinoma in noncirrhotic nonfibrotic liver with no viral hepatitis or alcohol abuse. *World J Surg* 2008; **32**: 104.
21. Lang H, Sotiropoulos GC, Brokalaki EI, *et al.* Survival and recurrence rates after resection for hepatocellular carcinoma in noncirrhotic livers. *J Am Coll Surg* 2007; **205**: 27.
22. Capussotti L, Muratore A, Amisano M, Massucco P, Polastri R, Bouzari H. Liver resection for large-size hepatocellular carcinomas in 47 non-cirrhotic patients – no mortality and long-term survival. *Hepatogastroenterology* 2006; **53**: 768.
23. Eguchi S, Ijtsma AJ, Slooff MJ, *et al.* Outcome and pattern of recurrence after curative resection for hepatocellular carcinoma in patients with a normal liver compared to patients with a diseased liver. *Hepatogastroenterology* 2006; **53**: 592.
24. Fong Y, Sun RL, Jarnagin W, Blumgart LH. An analysis of 412 cases of hepatocellular carcinoma at a Western center. *Ann Surg* 1999; **229**: 790. Discussion 9–800.
25. Llovet JM, Bruix J. Novel advancements in the management of hepatocellular carcinoma in 2008. *J Hepatol* 2008; **48**(Suppl. 1): S20.
26. Leung TW, Tang AM, Zee B, *et al.* Factors predicting response and survival in 149 patients with unresectable hepatocellular carcinoma treated by combination cisplatin, interferon-alpha, doxorubicin and 5-fluorouracil chemotherapy. *Cancer* 2002; **94**: 421.
27. Mergental H, Adam R, Klempnauer JL, *et al.* Liver transplantation as a rescue therapy for intrahepatic recurrence of hepatocellular carcinoma in non-cirrhotic livers after partial liver resection. *Transpl Int* 2007; **20**(Suppl. 2): 5. (abstract O012).
28. Hemming AW, Langer B, Sheiner P, Greig PD, Taylor BR. Aggressive surgical management of fibrolamellar hepatocellular carcinoma. *J Gastrointest Surg* 1997; **1**: 342.
29. Pinna AD, Iwatsuki S, Lee RG, *et al.* Treatment of fibrolamellar hepatoma with subtotal hepatectomy or transplantation. *Hepatology* 1997; **26**: 877.
30. El-Gazzaz G, Wong W, El-Hadary MK, *et al.* Outcome of liver resection and transplantation for fibrolamellar hepatocellular carcinoma. *Transpl Int* 2000; **13**(Suppl. 1): S406.
31. Jonas S, Steinmuller T, Settmacher U, Langrehr J, Muller A, Neuhaus P. Liver transplantation for recurrent hepatocellular carcinoma in Europe. *J Hepatobiliary Pancreat Surg* 2001; **8**: 422.
32. Margarit C, Charco R, Hidalgo E, Allende H, Castells L, Bilbao I. Liver transplantation for malignant diseases: selection and pattern of recurrence. *World J Surg* 2002; **26**: 257.
33. Hess D, Humar A, Sielaff TD. Living related liver transplantation for recurrent hepatocellular carcinoma in a normal liver. *Clin Transplant* 2002; **16**: 240.
34. Slater K, Bak TE, Kam I, Wachs ME. Living donor liver transplant for fibrolamellar hepatocellular carcinoma using a deceased donor graft to reconstruct inferior vena cava. *Liver Transpl* 2004; **10**: 555.
35. Malago M, Sotiropoulos GC, Nadalin S, *et al.* Living donor liver transplantation for hepatocellular carcinoma: a single-center preliminary report. *Liver Transpl* 2006; **12**: 934.
36. Onaca N, Davis GL, Jennings LW, Goldstein RM, Klintmalm GB. Improved results of transplantation for hepatocellular carcinoma: a report from the international registry of hepatic tumors in liver transplantation. *Liver Transpl* 2009; **15**: 574.

