Original article

Liver resection for hepatocellular carcinoma in non-cirrhotic liver without underlying viral hepatitis

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Background: **Hepatocellular carcinoma (HCC) arising in normal liver parenchyma is rare and the outcome after hepatectomy is not well documented.**

Methods: **Between June 1998 and September 2003, 33 patients without viral hepatitis underwent resection for HCC in a non-cirrhotic, non-fibrotic liver. Data were analysed with regard to operative details, pathological findings including completeness of resection, and outcome as measured by tumour recurrence and survival.**

Results: **Twenty-three major hepatectomies and ten segmentectomies or bisegmentectomies were performed. After potentially curative resection, 19 of 29 patients were alive at a median follow-up of 25 months, with calculated 1- and 3-year survival rates of 87 and 50 per cent respectively. Survival was significantly better after resection of tumours without vascular invasion (3-year survival rate 89 *versus* 18 per cent; $P = 0{\cdot}024$). Disseminated recurrence developed in nine of 29 patients, leading to death within 28 months of operation in all but one of the nine.**

Conclusion: **These data justify hepatic resection for HCC arising in non-cirrhotic, non-fibrotic liver without underlying viral hepatitis. Liver transplantation is rarely indicated because the outcome is good after resection of tumours without vascular infiltration, whereas vascular invasion is invariably associated with diffuse extrahepatic recurrence.**

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Introduction

Liver cirrhosis, particularly the macronodular variety, and viral hepatitis B and C are major risk factors for hepatocellular carcinoma (HCC) and have been found in up to 90 per cent of patients with HCC in Western countries[1–5]. In contrast, there are few data on HCC in non-cirrhotic and non-fibrotic liver because, except for the fibrolamellar variant, such tumours are rarely considered separately in published reports of HCC[6–9].

The clinical presentation and management of HCC depends on whether the liver is cirrhotic and whether there is underlying viral hepatitis. The prognosis of patients undergoing hepatectomy for HCC arising in normal hepatic parenchyma is not well documented. The aim of this study was to analyse surgical treatment and outcome in a consecutive series of patients without viral hepatitis undergoing partial hepatectomy for HCC in non-cirrhotic, non-fibrotic liver.

Patients and methods

Between June 1998 and September 2003, 33 patients (nine women and 24 men; median age 62 (range 24–79) years) with HCC in otherwise non-diseased liver underwent resection with curative intent. The diagnosis of HCC was based on histological examination of the resected specimen. Patients with liver cirrhosis, liver fibrosis, mixed HCC–cholangiocellular carcinoma, or underlying viral

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hepatitis B and C were excluded. There was no evidence of haemochromatosis or Wilson's disease.

Preoperative investigations performed to exclude extrahepatic tumour spread included abdominal ultrasonography, computed tomography (CT), chest radiography and, in selected patients, thoracic CT. Intraoperative ultrasonography was used routinely during liver resection.

No patient was lost to follow-up; data were complete to 15 December 2003. Survival was calculated using the Kaplan–Meier method, with statistical significance determined by the log rank test. $P < 0{\cdot}050$ was considered significant.

The following data were collected retrospectively: preoperative information including presenting symptoms, levels of biochemical markers and preoperative therapy; operative data such as extent of liver resection, vascular occlusion, transfusion requirement and postoperative complications; pathological data including completeness of surgical resection and tumour stage; and outcome measured in terms of incidence and treatment of tumour recurrence and survival.

Results

The main symptoms at presentation were abdominal pain and discomfort (22 of 33 patients), palpable tumour mass (eight patients), weight loss (four) and jaundice (one). Tumours were diagnosed in four patients at routine abdominal ultrasonography.

Preoperative tumour biopsy revealed the presence of HCC in 15 patients. In one patient with two large liver tumours, biopsy of one nodule led to a diagnosis of focal nodular hyperplasia (FNH). The second nodule was diagnosed as HCC at final histological examination. The serum α-fetoprotein level was measured in 21 of the 33 patients; it was raised in 15 patients to a median of 1050 (range 12–330 000) ng/ml (normal value less than 5 ng/ml).

In three patients HCC had been treated before resection, by chemoembolization in two patients and by injection of ethanol plus chemotherapy with cisplatin (Platinex®; Bristol-Myers Squibb, Munich, Germany) and epirubicin (Farmorubicin®; Pharmacia, Erlangen, Germany) in one patient. In two other patients, right portal vein ligation had been performed in the 2 months before hepatectomy.

Details of liver resections and additional procedures are shown in *Table 1*. Most patients required hemihepatectomy or extended hemihepatectomy. Dissection of regional lymph nodes was performed routinely. For one extended left hepatectomy, the operation included reconstruction of the segment VI vein to prevent congestion of the inferior right posterior sector. This area was at risk during left hepatectomy because of anomalous venous drainage of segment VI via the middle hepatic vein[11].

Intraoperative data are summarized in *Table 2*. Total vascular exclusion of the liver was used in five patients to control severe haemorrhage due to retrograde venous bleeding. One liver resection was performed with total vascular exclusion, femoroportoaxillary venovenous bypass and *in situ* protection by hypothermic perfusion, because of complex reconstruction of the inferior vena cava. The median transfusion requirement was 0 (range 0–14) units of packed red blood cells; 13 patients required between 2 and 14 units.

Two patients died within 30 days of surgery, one from pulmonary embolism 3 days after liver resection

Table 1 Operative procedures

	No. of patients ($n = 33$)
Resections	
Extended right hepatectomy	8
Extended right hepatectomy + wedge resection of segment III	1
Extended left hepatectomy	3
Extended left hepatectomy + wedge resection of segment VI	1
Right hepatectomy	5
Left hepatectomy	4
Central bisegmentectomy	1
Bisegmentectomy	5
Segmentectomy	5
Additional procedures	
Resection of hilar bifurcation	1
Partial resection of diaphragm	3
Partial resection of vena cava	1
Resection and reconstruction of segment VI vein	1

Liver resections were classified according to the Brisbane 2000 terminology of liver anatomy and resections[10].

Table 2 Details of vascular occlusion

	No. of patients ($n = 33$)	Duration of clamping (min)*	
		Portal vein	Caval vein
Hilar vascular occlusion only	19	20 (8–35)	—
Total vascular occlusion	5	24 (4–27)	22 (4–23)
Hypothermic *in situ* perfusion and femoroportoaxillary venovenous bypass	1	58†	58†
No vascular occlusion	8	—	—

*Values are median (range); †actual duration in one patient.

involving a venovenous bypass and the other from sepsis leading to multiple organ failure 22 days after extended right hepatectomy. Reoperation (two patients) and/or percutaneous intervention (six) was required in seven patients because of bile leakage (three) and intra-abdominal abscess (five) (one patient had both complications).

Median tumour diameter was 8 (range 2·5–17) cm (*Table 3*). Multifocal lesions were found in seven patients. Twenty-nine patients had an R0 and four an R1 resection. In one patient HCC was associated with simultaneous FNH. There was no fibrolamellar HCC.

Vascular infiltration was present in 16 patients, including 12 with microvascular infiltration only, three with macrovascular invasion only and one patient with both. Macrovascular infiltration included invasion of a major hepatic vein (three patients) and/or right portal trunk (one). Only one patient had regional lymph node metastasis. Tumours were highly, moderately and poorly differentiated in five, 20 and eight patients respectively. Vascular invasion was associated with moderately or poorly differentiated tumours only. Tumour stage according to recent (fifth edition) and current (sixth edition, 2002) Union Internacional Contra la Cancrum (UICC) classifications[12,13] is shown in *Table 3*. R0 resection was achieved for all stage I tumours (sixth edition). R1 resections were associated with multifocal tumours in three patients. In the patient with the two nodules suspected to be FNH (one of which was finally confirmed as HCC), tumour reached the surgical margin along the remaining right liver vein after extended left hepatectomy.

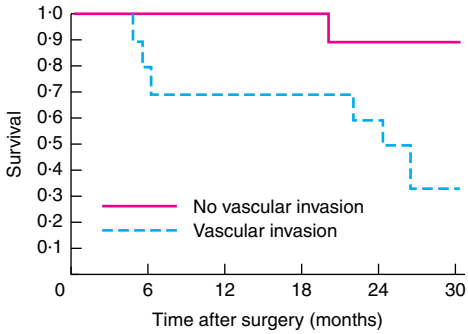
Table 3 Pathological findings

	No. of patients ($n = 33$)
Tumour size (cm)*	8 (2·5–17)
No. of lesions	
Solitary	26
Multifocal	7
Vascular invasion	
No	17
Yes	16
Microvascular invasion	12
Microvascular and macrovascular invasion	1
Macrovascular invasion	3
Regional lymph node involvement	1
Tumour grade	
G1	5
G2	20
G3	8
UICC TNM stage	
5th edition	
I	0
II	14
IIIA	10
IIIB	1
IVA	8
6th edition	
I	14
II	8
IIIA	7
IIIB	3
IIIC	1

*Values are median (range). UICC, Union Internacional Contra la Cancrum; TNM, tumour node metastasis.

Overall cumulative 1- and 3-year survival rates after hepatic resection were 76 and 38 per cent respectively. After R0 resection, 19 of 29 patients were alive at a median follow-up of 25 (range 0–64) months, with calculated 1- and 3-year survival rates of 87 and 50 per cent respectively. Excluding the two patients who died within 30 days of operation, survival after R0 resection was significantly poorer in those who had vascular infiltration than in those who did not ($P = 0·024$) (*Fig. 1*). After R1 resection, all four patients died from tumour recurrence between 7 and 25 months after operation.

No patient received adjuvant chemotherapy. Tumour recurrence developed in nine of 29 patients at a median of 10 (range 1–24) months after R0 resection. Microscopic or macroscopic vascular infiltration of the primary HCC had been present in eight patients, and tumour-positive lymph nodes in one patient. All nine patients had disseminated extrahepatic recurrence and six had additional intrahepatic lesions. Recurrence was treated by chemotherapy in all patients, with additional chemoembolization in one. One patient was alive with multifocal tumour spread 26 months after resection. The remaining eight patients died a median of 21 (range 5–28) months after resection.



No. at risk

No vascular invasion	16	11	10
Vascular invasion	11	7	5

Fig. 1 Survival after R0 resection of hepatocellular carcinoma in 27 patients with a non-cirrhotic, non-fibrotic liver and no underlying viral hepatitis, stratified according to the presence of vascular invasion. $P = 0·024$ (log rank test)

Discussion

Numerous studies have addressed the value of liver resection in HCC[14–25], but most data relate to patients with liver cirrhosis; those without cirrhosis have rarely been considered separately. Moreover, it is difficult to compare data between studies because different selection criteria have been used, in particular with respect to risk factors such as viral hepatitis, and because tumours have not always been staged according to the UICC classification[8,9,26]. To exclude the influence of concomitant liver disease on patient survival and tumour recurrence, patients with liver cirrhosis and those with HCC associated with viral hepatitis were not included in the present analysis.

The natural course of HCC arising in normal liver parenchyma cannot be assumed to be similar to that in patients with HCC in cirrhotic liver (survival less than 1 year after diagnosis without treatment)[27–29], because the complications of liver cirrhosis and portal hypertension contribute to the disease process in such patients.

The chance of long-term survival in the present series was particularly good in patients with solitary tumours without vascular invasion. Vascular infiltration was a significant risk factor for tumour recurrence and poor survival. These criteria might potentially be used for the preoperative identification of patients who are likely to benefit from surgery and the selection of suitable candidates for adjuvant therapy, although microvascular invasion is difficult to predict before surgery. Vascular infiltration was associated only with moderately or poorly differentiated tumours in this study, but routine preoperative tumour biopsy is not recommended because of its low predictive value for vascular infiltration and the potential risk of needle-track seeding[30]. The presence of multifocal tumour may prove to be a better indicator as this was frequently associated with vascular invasion (in five of seven patients). A larger study is required to confirm whether a combination of tumour size, grade and multifocal appearance serves as a surrogate marker of microvascular infiltration, as in HCC associated with cirrhosis[31]. The present data, however, showed no correlation between tumour size and vascular invasion. In the absence of reliable prognostic criteria, surgery should be considered if there is a chance of complete tumour removal.

The incidence of lymph node involvement was extremely low in the present study. Lack of such spread was associated with suitability for liver transplantation in a previous study of HCC in cirrhosis[32]. The liver is by far the most common site of recurrence after transplanation for HCC associated with cirrhosis, whereas recurrence involved diffuse extrahepatic spread in all patients in the present series. Haematogenous tumour cell dissemination was therefore the predominant route of metastasis, consistent with the finding that tumour recurrence was closely associated with vascular invasion. Tumour cells may have been disseminated during liver resection or, more probably, were already in the systemic circulation before liver resection[33]. It is therefore unlikely that tumour recurrence could have been avoided by more radical surgery, such as total hepatectomy. This pattern of metastasis would also mitigate against the use of transplantation, in contrast to the situation in cirrhosis. A possible exception might be the patient with late and irresectable recurrence confined to the liver. This is consistent with the results of Schlitt *et al.*[34], who noted a significantly higher rate of tumour recurrence after transplantation for HCC in non-cirrhotic compared with cirrhotic liver. Studies comparing liver transplantation and resection for HCC in non-cirrhotic liver have also shown a higher rate of recurrence after transplantation, probably due to immunosuppression[3,6,7,17,35–37].

References

1 Kew MC, Popper H. Relationship between hepatocellular carcinoma and cirrhosis. *Semin Liver Dis* 1984; **4**: 136–146.
2 Okuda K. Hepatocellular carcinoma: recent progress. *Hepatology* 1992; **15**: 948–963.
3 Farmer DG, Rosove MH, Shaked A, Busuttil RW. Current treatment modalities for hepatocellular carcinoma. *Ann Surg* 1994; **219**: 236–247.
4 Dürr R, Caselmann WH. Carcinogenesis of primary liver malignancies. *Langenbecks Arch Surg* 2000; **385**: 154–161.
5 Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet* 2003; **362**: 1907–1917.
6 Ringe B, Wittekind C, Weimann A, Tusch G, Pichlmayr R. Results of hepatic resection and transplantation for fibrolamellar carcinoma. *Surg Gynecol Obstet* 1992; **175**: 299–305.
7 Pinna AD, Iwatsuki S, Lee RG, Todo S, Madariaga JR, Marsh JW *et al.* Treatment of fibrolamellar hepatoma with subtotal hepatectomy or transplantation. *Hepatology* 1997; **26**: 877–883.
8 Bismuth H, Chiche L, Castaing D. Surgical treatment of hepatocellular carcinomas in noncirrhotic liver: experience with 68 liver resections. *World J Surg* 1995; **19**: 35–41.
9 Nagasue N, Yamanoi A, el-Assal ON, Ohmori H, Tachibana M, Kimoto T *et al.* Major compared with limited hepatic resection for hepatocellular carcinoma without underlying cirrhosis: a retrospective analysis. *Eur J Surg* 1999; **165**: 638–646.
10 Strasberg SM, Belghiti J, Clavien PA, Gadzijev E, Garden OJ, Lau WY *et al.* The Brisbane 2000 terminology of liver anatomy and resections. *HPB Surg* 2000; **2**: 333–339.
11 Lang H, Radtke A, Liu C, Frühauf NR, Peitgen HO, Broelsch CE. Extended left hepatectomy – modified

operation planning based on three-dimensional visualization of liver anatomy. *Langenbecks Arch Surg* 2004; **389**: 306–310.
12 Sobin LH, Wittekind C (eds). *TNM Classification of Malignant Tumours* (5th edn). Wiley-Liss: New York, 1997.
13 Sobin LH, Wittekind C (eds). *TNM Classification of Malignant Tumours* (6th edn). Wiley-Liss: New York, 2002.
14 Fong Y, Sun RL, Jarnagin W, Blumgart LH. An analysis of 412 cases of hepatocellular carcinoma at a Western center. *Ann Surg* 1999; **229**: 790–800.
15 Vauthey JN, Klimstra D, Franceschi D, Tao Y, Fortner J, Blumgart L *et al*. Factors affecting long-term outcome after hepatic resection for hepatocellular carcinoma. *Am J Surg* 1995; **169**: 28–35.
16 Takenaka K, Kawahara N, Yamamoto K, Kajiyama K, Maeda T, Itasaka H *et al*. Results of 280 liver resections for hepatocellular carcinoma. *Arch Surg* 1996; **131**: 71–76.
17 Iwatsuki S, Starzl TE, Sheahan DG, Yokoyama I, Demetris AJ, Todo S *et al*. Hepatic resection *versus* transplantation for hepatocellular carcinoma. *Ann Surg* 1991; **214**: 221–229.
18 Kanematsu T, Furui J, Yanaga K, Okudaira S, Shimada M, Shirabe K. A 16-year experience in performing hepatic resection in 303 patients with hepatocellular carcinoma: 1985–2000. *Surgery* 2002; **131**(Suppl): S153–S158.
19 Poon RTP, Fan ST, Ng IOL, Wong J. Significance of resection margin in hepatectomy for hepatocellular carcinoma: a critical reappraisal. *Ann Surg* 2000; **231**: 544–551.
20 Wei AC, Poon RTP, Fan ST, Wong J. Risk factors for perioperative morbidity and mortality after extended hepatectomy for hepatocellular carcinoma. *Br J Surg* 2003; **90**: 33–41.
21 Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, Yeung C *et al*. Hepatectomy for hepatocellular carcinoma: toward zero hospital deaths. *Ann Surg* 1999; **229**: 322–330.
22 Takano S, Oishi H, Kono S, Kawakami S, Nakamura M, Kubota N *et al*. Retrospective analysis of type of hepatic resection for hepatocellular carcinoma. *Br J Surg* 2000; **87**: 65–70.
23 Cha C, Fong Y, Jarnagin WR, Blumgart LH, DeMatteo RP. Predictors and patterns of recurrence after resection of hepatocellular carcinoma. *J Am Coll Surg* 2003; **197**: 753–758.
24 Takada Y, Otsuka M, Todoroki T, Fukao K. Accompanying liver cirrhosis as a risk factor for recurrence after resection of solitary hepatocellular carcinoma. *Hepatogastroenterology* 2003; **50**: 1991–1995.
25 Regimbeau JM, Abdalla EK, Vauthey JN, Lauwers GY, Durand F, Nagorney DM *et al*. Risk factors for early death due to recurrence after liver resection for hepatocellular carcinoma: results of a multicenter study. *J Surg Oncol* 2004; **85**: 36–41.
26 Ko S, Nakajima Y, Kanehiro H, Hisanaga M, Aomatsu Y, Kin T *et al*. Significant influence of accompanying chronic hepatitis status on recurrence of hepatocellular carcinoma after hepatectomy. Result of multivariate analysis. *Ann Surg* 1996; **224**: 591–595.
27 Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso MDC, Sala M *et al*. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. *Hepatology* 1999; **29**: 62–67.
28 Herold C, Reck T, Fischler P, Ott R, Radespiel-Troeger M, Ganslmayer M *et al*. Prognosis of a large cohort of patients with hepatocellular carcinoma in a single European centre. *Liver* 2002; **22**: 23–28.
29 Christians KK, Pitt HA, Rilling WS, Franco J, Quiroz FA, Adams MB *et al*. Hepatocellular carcinoma: multimodality management. *Surgery* 2001; **130**: 554–559.
30 Fiore F, Daniele B, De Maio E, Tambaro R, Iaffaioli VR, Barbarisis A *et al*. Subcutaneous seeding of hepatocellular carcinoma after fine-needle percutaneous biopsy. *J Clin Gastroenterol* 2001; **33**: 171.
31 Jonas S, Bechstein WO, Steinmüller T, Herrmann M, Radke C, Berg T *et al*. Vascular invasion and histopathologic grading determine outcome after liver transplantation for hepatocellular carcinoma in cirrhosis. *Hepatology* 2001; **33**: 1080–1086.
32 Klintmalm GB. Liver transplantation for hepatocellular carcinoma: a registry report of the impact of tumor characteristics on outcome. *Ann Surg* 1998; **228**: 479–490.
33 Sheen IS, Jeng KS, Shih SC, Wang PC, Chang WH, Wang HY *et al*. Does surgical resection of hepatocellular carcinoma accelerate cancer dissemination? *World J Gastroenterol* 2004; **10**: 31–36.
34 Schlitt HJ, Neipp M, Weimann A, Oldhafer KJ, Schmoll E, Boeker K *et al*. Recurrence patterns of hepatocellular and fibrolamellar carcinoma after liver transplantation. *J Clin Oncol* 1999; **17**: 324–331.
35 Pichlmayr R, Weimann A, Oldhafer K, Schlitt HJ, Klempnauer J, Bornscheuer A *et al*. Role of liver transplantation in the treatment of unresectable liver cancer. *World J Surg* 1995; **19**: 807–813.
36 Neuhaus P, Jonas S, Bechstein WO, Wex C, Kling N, Settmacher U *et al*. Liver transplantation for hepatocellular carcinoma. *Transplant Proc* 1999; **31**: 469–471.
37 Neuhaus P, Jonas S, Bechstein WO. Hepatoma of the liver – resection or transplantation? *Langenbecks Arch Surg* 2000; **385**: 171–178.