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Outcome of liver resection and transplantation for fibrolamellar hepatocellular carcinoma

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Abstract Fibrolamellar hepatocellular carcinoma (FL HCC) is an uncommon variant of hepatocellular carcinoma occurring usually in non-cirrhotic livers. Hepatic resection or transplantation offers the only chance of cure. We reviewed our experience of surgery for FL HCC from 1985–1998. Twenty patients with FL HCC (13 females and 7 males) median age 27 years (range 12–69) were treated either by hepatic resection [$n = 11$; extended right hepatectomy (5), extended left hepatectomy (1), right hemihepatectomy (2), left hemihepatectomy (2), left lateral segmentectomy (1)] or, if the disease was non-resectable, by transplantation ($n = 9$). The median follow up was 25 months (1–63). The prognostic factors analysed included size [less than 5 cm (3 patients), more than 5 cm (17 patients)], number [solitary (16 patients), multiple (4 patients)], capsular invasion (6 patients), vascular invasion (11 patients) and lymph node invasion (6 patients). The overall survival at 1, 3 and 5 years was 89.5, 75 and 50%, respectively. The liver resection survival was better than liver transplantation survival at 3 years 100 vs 76%, respectively ($P < 0.025$). Although all prognostic factors analysed did not show a significant difference, there is tendency that tumour stage was the most significant for prognosis. Most of the patients in this study are young and presented without specific symptoms, with normal liver function range and had no tumour marker to help in diagnosis. As a result most of our patients were diagnosed late. However the outcome of surgical intervention was favourable.

Key words Fibrolamellar hepatocellular carcinoma · Liver resection · Liver transplantation

Introduction

Fibrolamellar hepatocellular carcinoma (FLHCC) has been recognised as a distinct type of hepatocellular carcinoma (HCC), which may have a more favourable prognosis. Patients with FLHCC have been reported to have a higher resectability rate and also prolonged survival time after resectional therapy compared to HCC [10]. Well differentiated lesions, grade I or II, as described by Edmondson and Steiner [6], have an important bearing on survival, with 1-year survival of 76% for grade I + II vs 23% for grade III + IV [15]. FL HCC and early stages of HCC were highly represented among the long-term survivors [9].

Fibrolamellar HCC enjoys most-favoured cancer status and, when unresectable but confined to the liver, is considered a suitable indication for liver transplantation by most investigators [8]. Longer disease-free intervals and prolonged survival after recurrence in patients with FLHCC as compared to those with non-FLHCC have been repeatedly demonstrated. [4]. In this context we reported our experience in 20 patients with this uncommon variant of HCC who were treated between 1985 and 1998. Our aims were to determine the overall

Table 1 Presenting symptoms of patients with fibrolamellar hepatocellular carcinoma (FLHCC)

Presentation	Number
Abdominal pain	10
Weight loss	8
Liver mass	6
Ascites and lower oedema	1
Jaundice	1

prognosis and to identify certain prognostic criteria, as well as to emphasis the role of hepatic resection and transplantation in treatment.

Patients and methods

From 1982 to 1998, 125 patients with HCC, proven on histology, were treated by partial hepatectomy or orthotopic liver transplantation at the Birmingham Liver Unit. Of these, 20 patients (13 females, 7 males; median age 27 years, range 12–69) with FLHCC were identified and form the basis of this series. Table 1 shows the presenting symptoms of patients with FLHCC. Preoperative liver function tests were normal except in 1 patient where there was a mild increase in the serum transaminase and bilirubin levels with a decrease in the serum albumin level. The serum alpha-fetoprotein level was normal in all patients. Hepatitis B status was determined in 13 patients and was negative. None of patients had associated cirrhosis of liver.

Tumour size was more than 10 cm in 13 patients. Vascular invasion was present in 11 patients and 7 of them had major vessels invasion [portal vein (5), hepatic artery (1), hepatic vein (1)]. The tumuor was solitary in 16 patients (80%) and multiple in 4 patients (20%). Six patients had lymph node involvement. By using the TNM classification as proposed by the International Union Against Cancer (UICC), there were 6 patients stage II, 5 patients stage III and 9 patients stage V.

From 20 patients, 11 (3 males and 8 females) underwent partial hepatectomy [extended right hepatectomy (5), extended left hepatectomy (1), right hemihepatectomy (2), left hemihepatectomy (2), left lateral segmentectomy (1)]. One patient had extrahepatic spread in the porta hepatis, the resection margin was positive in 2 patients and the margin of clearance was less than 0.5 cm in 8 patients. Nine patients (3 males and 6 females) with non-resectable disease underwent standard liver transplantation, due to either centrally located tumours or to close proximity of the tumour to the hilar vessels. Five patients had vascular invasion, 3 patients had tumour in the lymph nodes and tumour stages III and IV were found in 6 patients (66%).

The median follow up was 25 months for resected cases and 35 months for transplanted cases. Table 2 and Figs. 1 and 2 showed other clinical and pathological features of both groups of patients. Prognostic factors analysed included size, number, capsular invasion, vascular invasion, lymph node invasion and bilobar involvement. The mean blood transfusion intraoperative was 9 units (0–25). Two patients received chemotherapy after surgery. For statistical analysis, survival data and comparison of non-continous variables between groups was obtained by the chi-squared test. Survival and recurrence-free rates were calculated using the method of Kaplan-Meier and the logrank test. Statistical significance was considered at $P < 0.05$.

Table 2 Clinicopathological characteristics of 20 patients with FLHCC. (*F* female, *M* male, *LN* lymph nodes, *ERHH* extended right hepatectomy, *ELHH* extended left hepatectomy, **RHH** right hepatectomy, **LHH** left hepatectomy, *L. Segm* left segmentectomy, *Y* yes, *N* no, *OLT* liver transplantation, *Pt* patient)

Pt	Age (years)	Sex	Operation	Size (cm)	Bilobular	LN	Number	Vascular invasion	Capsular ulceration	Stage	Recurrence (site)	Survival (months)[a]
1	17	M	OLT	11	Y	N	1	Y	N	IV	N	55.83
2	12	F	OLT	14	Y	Y	1	N	N	IV	N	31.13
3	37	F	OLT	19	Y	N	1	Y	N	IV	N	33.70
4	27	F	OLT	8	N	N	1	N	N	II	N	0
5	21	F	OLT	4	N	N	1	N	N	II	Y (spine)	2
6	19	F	OLT	9, 2	N	N	2	Y	Y	III	Y (liver)	20
7	18	F	OLT	15, 11	Y	Y	2	Y	Y	IV	Y (liver and lung)	26
8	23	M	OLT	7	N	N	1	N	N	II	Y (lung)	63.03
9	21	M	OLT	16, 12, 3	Y	Y	3	Y	Y	IV	Y (spine)	7.33
10	28	F	ERHH	10	N	N	1	N	N	II	N	39.97
11	69	F	L. Segm	2	N	N	1	N	N	II	N	5.27
12	19	F	ELHH	7.5	Y	Y	1	Y	Y	IV	Y (liver)	23.00
13	20	M	ERHH	21	N	N	1	Y	N	IV	Y (liver)	33.60
14	29	F	RHH	22	N	N	1	Y	N	III	N	12.33
15	24	F	ERHH	20	Y	Y	1	Y	Y	IV	Y (spine)	27.27
16	33	F	LHH	20	N		1	Y	N	III	N	16.33
17	62	M	RHH	13	N	N	1	N	N	III	N	12.60
18	20	F	LHH	13	N	Y	1	Y	Y	IV	N	24.53
19	23	M	ERHH	5, 4	N	N	2	N	N	III	Y (liver)	32.73
20	19	M	ERHH	19	N	N	1	N	N	II	N	10.57

[a] At 2 February 1998

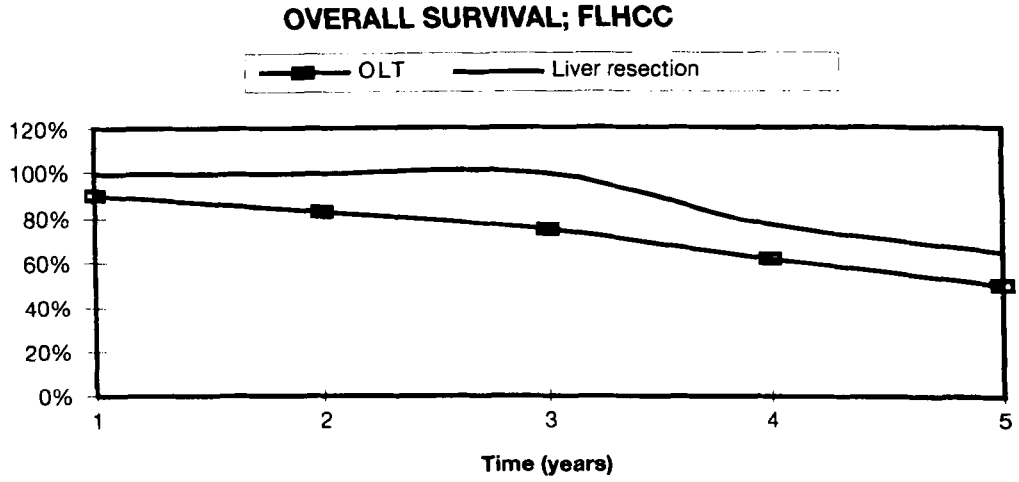

Fig. 1 Overall survival of patients with fibrolamellar hepatocellular carcinoma (FLHCC) following liver transplantation (*OLT*) or liver resection

Results

The overall survival at 1, 3 and 5 years was 89.5, 75 and 50%, respectively; median survival was 62 months. There was only one intraoperative death (5%) due to bleeding during liver transplantation in the early 1980s. Overall 1-, 3-, and 5-year survival in patients undergoing resection was 100, 100, and 65%, respectively, while it was 90, 75, and 50% in transplanted patients, respectively. Survival in patients undergoing liver resection was better than liver transplantation survival at 3 years 100 versus 76%, respectively ($P < 0.025$; Fig. 1). Prognostic factors analysed, including: size, number, capsular invasion, vascular invasion, lymph node invasion and bilobar involvement, were statistically insignificant ($P > 0.05$).

Four patients (1 before and after liver transplantation, 1 after liver transplantation, 2 after liver resection) received combined chemotherapy in the form of 5-fluorouracil, folic acid and cisplantinum. Chemotherapy had no detectable effect on survival or recurrence-free survival in those patients. Recurrence of the tumour occurred in 9 patients (45%) all of whom have died (5 transplanted and 4 resected). Ten patients are alive without tumour recurrence (3 were transplanted and 8 were resected patients). Recurrence occurred after a mean of 10 months (2–26) following hepatic resection and after a mean of 8 months (1–30) following liver transplantation.

Discussion

FLHCC forms a difficult problem in diagnosis, as most of the patients are young and present without specific symptoms and with normal liver function tests [1–3, 5]. Also alpha-fetoprotien is usually normal, without un-

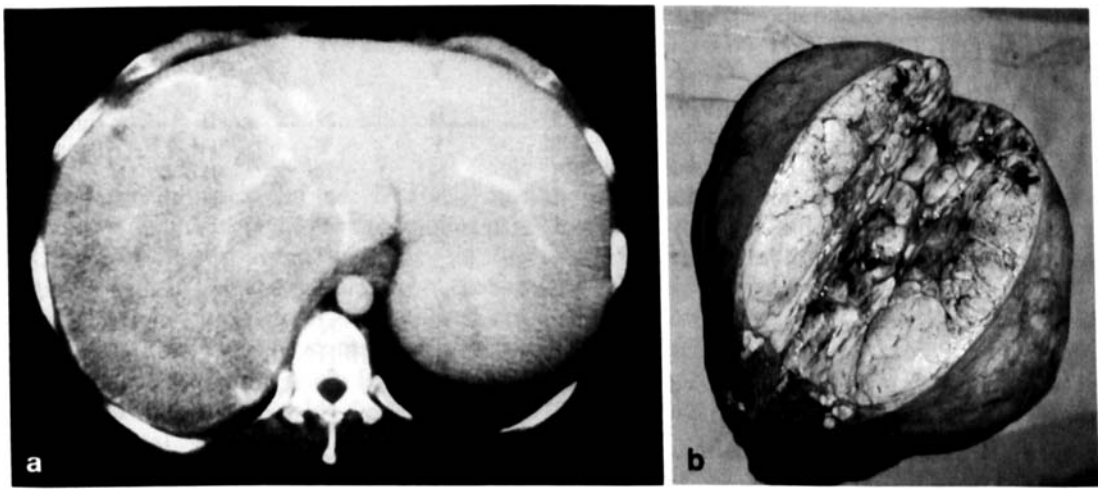

Fig. 2 CT (**a**) and postoperative specimen (**b**) from a 20-year old male patient with FLHCC who underwent extended right hepatectomy

derlying liver disease. As a result, most of the cases are diagnosed in an advanced stage and this has an impact on the outcome of treatment. FLHCC often presents as a large, solitary liver tumour. The mean tumour size is between 10 and 15 cm [18], with a range from 4 to over 20 cm. Unlike HCC that often presents with multiple lesions, a high percentage (55–65%) of patients with FLHCC have a solitary lesion [7–10]. Regional and distant metastases are present in approximately one-third of patients at the time of diagnosis [12]. The surrounding liver parenchyma is usually normal, unlike HCC which is often associated with chronic liver disease. Alpha-fetoprotien is reported to be normal in more than 90% of FLHCC cases in most of the studies, while elevation of Des-y-carboxy prothrombin, neurotensin and vitamin B12-binding capacity have been reported with FLHCC [11, 13].

In this report FLHCC achieved better survival rates when compared to regular HCC. Also our study supported the general impression that FLHCC is an indolent tumour, prevalent among young patients and not associated with chronic liver diseases or increase in serum alpha-fetoprotien. These findings are in accordance with previous reports [12–18]. Although the analysed prognostic factors in this study did not show any statistically significance difference, which may be because of the small number of patients, there is a tendency tumours that the early stages of development responded much better and this has an influence on the long-term outcome. Chemotherapy had no effect on survival or recurrence in the four patients who received chemotherapy after surgery. A few reports emphasised the effect of combined chemotherapy in regression of unresectable FLHCC thus enabling debulking surgery to be performed [11, 13].

In this study, patients who underwent partial hepatic resection did better than patients who underwent liver transplantation and this is in accordance with the Pittsburgh and Hanover reports [4, 15]. This may be due to the early stage of tumour in resected patients as most of the transplanted patients were unsuitable for resection because of advanced tumour stage or location of the tumour. Radical operations have offered optimal treatment for such patients; either liver resection or liver transplantation can achieve a curative goal [14]. In current reports, although more than two-thirds of our patients were stage III and IV, overall survival was better than regular HCC. Most of the patients in this study are young and presented without specific symptoms and with normal liver function range, as a result most of our patients were diagnosed late. However the outcome of surgical intervention was favourable. So we believe that even in advanced cases of FLHCC, aggressive surgical treatment, either liver resection if possible or liver transplantation, is justified. Also research is needed to help identify risk factors for the development of FLHCC and to develop suitable ways for early diagnosis.

References

1. Ang PT, Evans H, Pazdur R (1991) Fibrolamellar hepatocellular carcinoma. Am J Clin Oncol 14: 175–178
2. Berman MA, Burnham JA, Sheahan DG (1988) Fibrolamellar carcinoma of the liver: an immunohistochemical study of nineteen cases and a review of literature. Hum Pathol 19: 784–794
3. Bower M, Newlands ES, Habib N (1996) Fibrolamellar hepatocellular carcinoma responsive to platinum-based combination chemotherapy. Clin Oncol 8: 331–333
4. Busuttil RW, Farmer DG (1996) The surgical treatment of primary hepatobiliary malignancy. Liver Transplant Surg2: 114–130
5. Craig JR, Peters RL, Edmondoson HA, Omata M (1980) Fibrolamellar carcinoma of the liver: a tumour of adolescents and young adults with distinctive clinicopathological features. Cancer 46: 372–379
6. Edmondson HA, Steiner PE (1954) Primary carcinoma of the liver: a study of 100 cases among 48900 necropsies. Cancer 7: 462–503
7. Friedman AG, Lichtenstein JE, Goodman Z et al. (1985) Fibrolamellar hepatocellular carcinoma. Radiology 157: 583–587
8. Haug CE, Jenkins RL, Rohrer et al. RJ (1992) Liver transplantation for primary hepatic cancer. Transplantation 53: 376–382
9. Iwatsuki S, Starzl TE, Sheahan et al. DG (1991) Hepatic resection versus transplantation for hepatocellular carcinoma. Ann Surg 214: 221–228
10. Nagorney DM, Adson MA, Weiland LH, Knight CD Jr, Smally SR, Zinsmeister AR (1985) Fibrolamellar hepatoma. Am J Surg 149: 133–139
11. Paradinas FJ, Melia WM, Wilkinson ML, Protmann B, Johnson PJ, Murray-Lyon IM, Williams R (1982) High serum vitamin B12 binding capacity as a marker of the fibrolammelar variant of hepatocellular carcinoma. Br Med J 285: 840–842
12. Payne CM, Nagle RB, Paplanus SH, Graham AR (1986) Fibrolamellar carcinoma of the liver: a primary malignant oncocytic carcinoid? Ultrastruct Pathol 10: 539–552
13. Penna AD, Iwatuski S, Lee RG et al. (1997) Treatment of fibrolamellar hepatoma with subtotal hepatectomy or transplantatation. Hepatology 26: 877–883
14. Ring B, Wittekind C, Weimann A, Tusch G, Pichlmayr R (1992) Results of hepatic resection and transplantation for fibrolamellar carcinoma. Surg Gynecol Obstet 175: 299–305
15. Rosen CB, Nagorney DM (1994) Fibrolamellar and less aggressive hepatocellular carcinoma. In: Terblanche J (ed) Hepatobiliary malignancy: its multidisciplinary management. Edward Arnold, London, pp 204–212
16. Starzl TE, Iwatsuki S, Shaw BWJ, Nalesnik MA, Farhi DC, Van Thiel DH (1986) Treatment of fibrolamellar hepatoma with partial or total hepatectomy and transplantation of the liver. Surg Gynecol Obstet 162: 145–148
17. Saab S, Francis Y (1996) Fibrolamellar hepatocellular carcinoma: case reports and a review of literature. Dig Dis Sci 41: 1981–1985
18. Wood WJ, Rawlings M, Evans H, Lim CNH (1988) Hepatocellular carcinoma: importance of histological classification as a prognostic factor. Am J Surg 155: 663–666