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Liver Transplantation in the Treatment of Primary Liver Cancer

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Abstracts

One hundred and fifteen patients underwent orthotopic liver transplantation (OLT) for primary liver malignancy. Overall survivals of these patients were significantly lower than those of patients with non-malignant diseases (5-year survival rates 37% and 65%, respectively). Hepatocellular carcinoma (HCC) was the most common malignancy among our patients (n = 80). Fibrolamellar HCC (n = 9) was associated with better survival than non-fibrolamellar HCC (N = 71) among the lesions ≥ 5 cm in diameter. More frequent recurrence was noted in patients with large tumors (≥ 5 cm), multiple tumors, and gross vascular involvement. A significant lower survival rate was observed in patients with bile duct cancer (n = 19) than in those with HCC or epithelioid hemangioendothelioma (n = 8). Careful patient selection and effective adjuvant anticancer therapy are needed to improve the results of OLT for primary liver malignancy.

Key words

Liver - Transplantation - Cancer

The optimal treatment of primary liver malignancy is complete surgical excision of the tumors. Extensive subtotal hepatectomy such as right and left trisegmentectomies can now be performed with an operative mortality of less than 5% (1-4). We have already reported 1, 3 and 5-year survivals of 69, 45 and 32% after major subtotal hepatectomy for primary hepatic malignancy (4). There were, however, many other patients who could not be treated with subtotal hepatectomy, either because of extensive hepatic involvement with malignant tumor, or because of coexisting advanced liver disease. These patients had been carefully selected for total hepatectomy and liver replacement (orthotopic liver transplantation: OLT).

Our experience with OLT in the case of primary hepatic malignancy is summarized here in an attempt to examine the factors that influence survival and tumor recurrence.

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Table 1 Histological diagnosis of 115 patients with primary liver malignancy

Histology	Number of patients
Hepatocellular carcinoma	80
(Non-fibrolamellar)	(71)
(Fibrolamellar)	(9)
Bile duct cancer	19
Epithelioidhemangioendothelioma	8
Hepatoblastoma	4
Cholangiocarcinoma	2
Angiosarcoma	2
Total	115

Patient materials and methods

Between January 1980 and December 1988, 1,469 patients with various advanced liver diseases received orthotopic liver transplantation (OLT) at the University Health Sciences Center of Colorado (1980) and the University Health Center of Pittsburgh (since 1981). All of these patients were treated with a standard combination immunosuppressive therapy of cyclosporine and corticosteroids. Azathioprine antilymphocyte globulin or murine monoclonal antibody (OKT-3) was used supplementarily in selected patients to control rejection (5-7). Our surgical techniques have been reported in detail elsewhere (8-10).

One hundred and fifteen (7.4%) of the 1,469 patients received OLT for primary hepatobiliary malignancy. In 28 of the 115 patients, OLT was done to treat hepatic failure, but malignant tumors were discovered incidentally at the pathological examination of the excised liver ("incidental" malignancy). In the remaining 87 patients, the diagnosis of malignancy was established or strongly suspected before OLT. Total rather than subtotal hepatectomy was performed because of co-existing advanced liver disease in 34 patients (malignancy in advanced liver disease), and because of extensive tumor involvement no longer accessible to subtotal hepatectomy in 53 patients ("unresectable" tumor).

The histological diagnosis established in 115 primary hepatobiliary malignant tumors are listed in Table 1. There were 80 hepatocellular carcinomas (HCC), 19 bile duct cancers (BD Ca), 8 epithelioid hemangioendotheliomas (EHE), 4 hepatoblastomas (HBL), 2 cholangiocarcinomas, and 2 angiosarcomas. Nine of the 80 hepatocellular carcinomas were of the fibrolamellar type.

Non-cancerous advanced liver disease coexisted in 62 out of 115 patients with primary hepatobiliary malignancy, as shown in Table 2. Forty-four of the 80 patients with HCC had underlying advanced cirrhosis of various etiologies, including 22 patients with hepatitis B surface antigen (HBsAg). Sixteen of the 19 bile duct cancers developed in advanced primary sclerosing cholangitis. One patient had both bile duct cancer and metastatic carcinoid tumor.

All patients were followed up for a period ranging from 6 months to 9 years, with a mean of 25 months. Survival rates

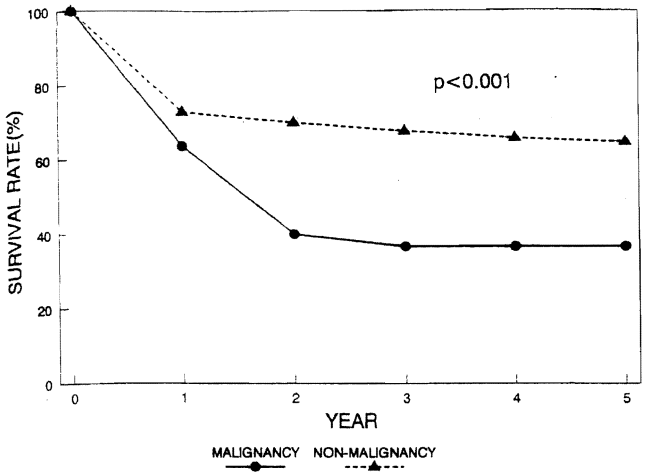

Fig. 1 1. Survival curves of patients with primary liver malignancy (n=115) and non-malignant diseases (n=1354) in the period 1980–1988

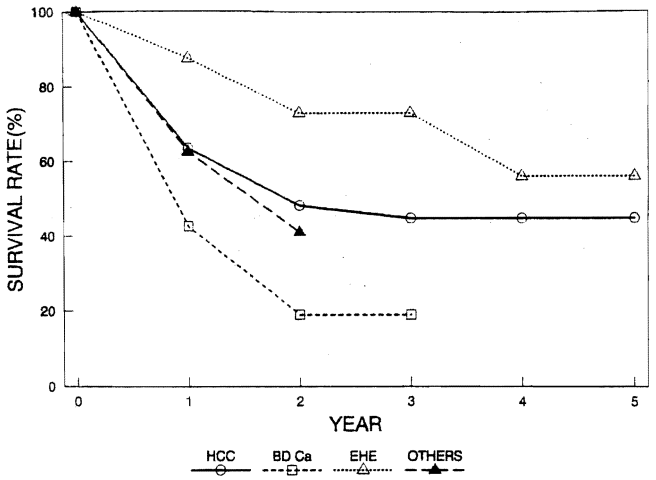

Fig. 2 2. Survival curves of various types of primary liver malignancy: hepatocellular carcinoma (HCC, n= 80), bile duct cancer (BD Ca) (n=19), epithelioid hemangioendothelioma (EHE) (n=8) and others: hepatoblastoma (n=4), cholangiocarcinoma (n=2) and angiosarcoma (n=2)

Table 2 Coexisting liver disease with various primary liver cancers

Diagnosis	Number of patients
Hepatocellular carcinoma (non-fibrolamellar)	
Cirrhosis:	
hepatitis B	22
non-A, non-B	2
alcoholic	2
autoimmune	1
cryptogenic	5
hemochromatosis	2
tyrosinemia	4
alfa 1 anti-trypsin deficiency	1
biliary atresia	2
Neville's disease	1
familial cholestasis	1
Hepatocellular carcinoma (fibrolamellar)	
Cirrhosis:	
cryptogenic	1
Bile duct cancer	
sclerosing cholangitis	16
metastatic carcinoid	1
Hepatoblastoma	
biliary atresia	1
	18
Total	62

Table 3 Cumulative survival rates in primary liver cancer

Primary liver cancer	Survival rates (%)		
	1 year	3 year	5 year
Hepatocellular carcinoma (n=80)			
Non-fibrolamellar (n=71)	64	45	45
Fibrolamellar (n=9)	89	46	46
Non-fibrolamellar, Tumor size < 5 cm (n=28)	77	68	68
Non-fibrolamellar, Tumor size ≥ 5 cm (n=43)	51	25	25
Bile duct cancer (n=19)	24	24	0
Epithelioid hemangioendothelioma (n=8)	88	73	48
Hepatoblastoma (n=4)	25	0	
Cholangiocarcinoma (n=2)	50	0	
Angiosarcoma (n=2)	0		

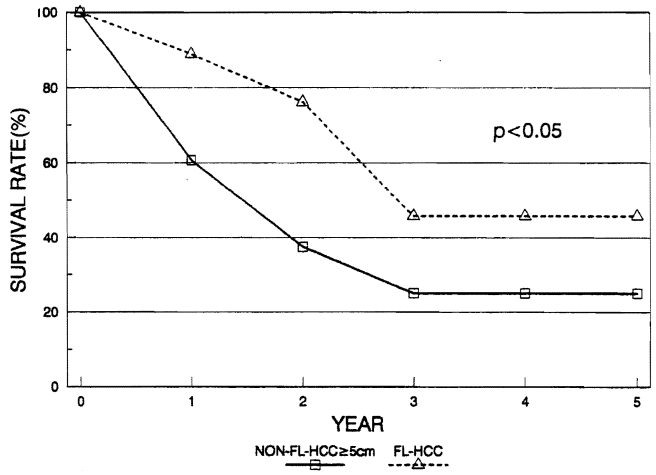

Fig. 3 Survival curves of fibrolamellar HCC (n=9) and non-fibrolamellar HCC with tumor ≥ 5 cm (n=43).

were calculated by the method of Kaplan-Meier. Statistical comparisons were made by the method of Mantel-Cox and by the Chi-squared test. The difference was considered significant when the p value was less than 0.05.

Results

Survival

The survival rates after OLT of the 115 patients with primary liver malignancy and the 1,354 patients without it were compared, and are shown in Fig. 1. One-, 3- and 5-year survival rates of the former were 64%, 37% and 37%, and those of the latter were 73, 68, and 65%, respectively. The survival rates of patients with primary hepatic malignancy were significantly lower than those of patients with no malignancy ($p < 0.001$).

Survival rates of the 115 patients with primary hepatic malignancy were stratified in accordance with the histological diagnosis of the tumors, and are compared in Table 3 and Fig. 2. Survival of patients with epithelioid hemangioendothelioma (EHE) seemed to be better than that of patients with hepatocellular carcinoma (HCC), but the difference was

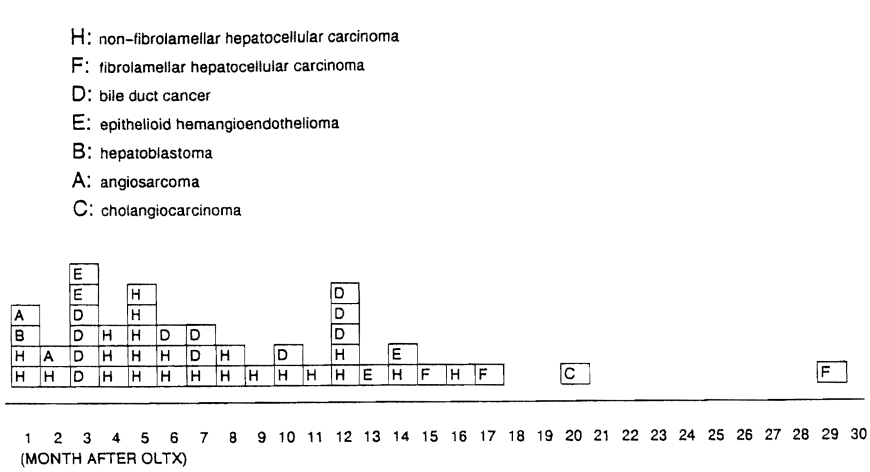

Fig. 4 Timing of recurrence in primary hepatic malignancy

Table 4 Survival rate and various factors in non-fibrolamellar hepatocellular carcinoma

Factor	Mean survival time (months) mean ± SE	Number of patients Deaths/Total	%
Tumor size			
< 5 cm (n=33)	55±8*	13/33	39
≥ 5 cm (n=38)	24±6	20 /38	56
Tumor number			
single (n=14)	81±11*	2/14	14
multiple (n=57)	34±6	31/57	56
Gross vascular invasion			
(+)(n=16)	18±6	12/16	75
(–)(n=55)	53±7*	22/55	42
Lymph node metastasis			
(+)(n= 7)	10±2	4/7	57
(–)(n=64)	48±6*	30/64	48

*The difference is statistically significant ($p < 0.05$)

not statistically significant ($p = 0.36$). Survival of patients with bile duct cancer (BD Ca) was significantly lower than that of patients with EHE ($p < 0.005$) or HCC ($p < 0.05$).

Survival rates of 80 patients with HCC were further analyzed in accordance with the histopathological findings. The survival of 9 patients with fibrolamellar variant was not significantly better than that of 71 patients with non-fibrolamellar hepatoma ($p = 0.3225$) (Table 3). However, when tumors less than 5 cm in the greatest diameter were excluded, survival of patients with fibrolamellar variant was significantly better than that of those with non-fibrolamellar hepatoma ($p < 0.05$) (Fig. 3, Table 3). The prognostic influence of other histopathological findings, such as the size and number of malignant lesions, gross vascular invasion of tumor and regional lymph node metastasis, was examined in the 71 patients with non-fibrolamellar hepatoma, and expressed in terms of mean survival time (Table 4). Small tumors less than 5 cm in the greatest diameter, and single lesions were statistically significant good prognostic factors ($p < 0.01$, $p < 0.005$, respectively). On the other hand, the presence of gross vascular invasion and regional node metastasis were significantly poor prognostic pathological findings ($p < 0.05$ and $p < 0.05$, respectively).

Tumor recurrence
Incidence, timing and location

Recurrence of original hepatic malignancy was confirmed in 45 of the 115 patients after OLT. Timing of recurrence is shown in Fig. 4. Tumor recurrence was diagnosed within 3 months after OLT in 12 patients. These very early recurrences were most likely due to residual tumors, which had not been properly removed by total hepatectomy, or not detected before OLT despite thorough investigation for distant metastasis. These very early recurrences were seen in 4 patients with BD Ca, 3 patients with hepatocellular carci-

Table 5 Initial and ultimate site of recurrence in primary liver cancer

Site	Diagnosis Initial (Ultimate)					
	HCC pts (pts)	BD Ca pts (pts)	EHE pts (pts)	HBL pts (pts)	AS pts (pts)	CC pts (pts)
Liver	9 (16)	2 (4)	1 (3)	0 (0)	0 (1)	1 (1)
Lung	9 (11)	1 (3)	0 (3)	1 (1)	1 (1)	0 (1)
Intra-abdominal (extrahepatic)	4 (6)	3 (5)	0 (0)	0 (0)	1 (1)	0 (0)
Bone	4 (6)	3 (3)	2 (2)	0 (0)	0 (1)	0 (0)
Brain	0 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Skin	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Mediastinum	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Total	26 (40)	11 (17)	4 (9)	1 (1)	2 (4)	1 (2)

*HCC: hepatocellular carcinoma, BD Ca: bile duct cancer, EHE: epithelioid hemangioendothelioma, HBL: hepatoblastoma, AS: angiosarcoma, CC: cholangiocarcinoma

Table 6 The influence of histopathological factors on tumor recurrence

Factor	Number of patients Recurrence/Total	Rate (%)	Statistics (P value)
1) Non-fibrolamellar	23/62	37	N.S.*
fibrolamellar	3/8	38	
non-fibrolamellar, tumor size ≥ 5 cm	21/34	62	N.S.*
fibrolamellar, tumor size ≥ 5 cm	3/8	38	
2) Non-fibrolamellar tumor size < 5 cm	2/28	20	< 0.0005
tumor size ≥ 5 cm	21/34	62	
3) Non-fibrolamellar single tumor	1/15	7	< 0.05
multiple tumor	22/47	47	
4) Non-fibrolamellar gross vascular invasion	8/11	73	< 0.05
no vascular invasion	15/51	29	
5) Non-fibrolamellar lymph node metastasis (+)	3/4	75	N.S.*
lymph node metastasis (–)	20/58	34	

N.S.*: not significant

noma, 2 patients with angiosarcoma, 2 patients with epithelioid hemangioendothelioma, and 1 patient with hepatoblastoma.

By one year after OLT an additional 25 patients developed tumor recurrences: these included 18 patients with HCC and 7 with bile duct cancer. Between 1 and 2 years after OLT, tumor recurrences were diagnosed in 4 patients with hepatocellular carcinoma (2 each of non-fibrolamellar and fibrolamellar hepatocellular carcinoma), 2 patients with epi-thelioid hemangioendothelioma, and 1 with cholangiocarcinoma. After 2 years another patient with fibrolamellar hepatocellular carcinoma developed recurrent tumor (Fig. 4).

The first location of recurrence and the organs ultimately involved by tumors were examined in the 45 patients according to the histological diagnosis of malignancy, and are summarized in Table 5. The transplated liver was the most common site of recurrence, followed by the lung.

Factors influencing tumor recurrence

Histopathological findings which might influence the tumor recurrence were examined in the 70 patients with HCC, who were rendered tumor-free at the time of OLT and who survived more than 3 months (Table 6). Three (38%) of the 8 patients with fibrolamellar hepatoma and 23 (37%) of the 62 patients with non-fibrolamellar hepatoma developed tumor recurrence. When the tumors of less than 5 cm in the greatest diameter were excluded, 21 out of 33 patients (64%)

Table 7 Cause and timing of death

Time / Cause of death	Diagnosis and number of patients: Hepato-cellular carcinoma	Bile duct cancer	Epithelioid-hemangio-endothelioma	Others (d)
< 3 months				
Operative death	1	0	0	0
Graft failure (a)	5	2	0	2 (1)*
Infection	3	0	0	1 (1)*
Lymphoma (b)	1	0	0	0
(total)	10	2	0	3
3–12 months				
Graft failure (a)	2	3 (2)*	0	0
Hepatitis B	3 (2)*	0	0	0
Infection	2	0	0	0
Malignancy	9	4	0	1
(total)	16	7	0	1
> 12 months				
Graft failure (a)	1	0	1	0
Hepatitis B	1	0	0	0
Lymphoma (b)	1	0	0	0
Malignancy	8	4	2	1
Others (c)	1	0	0	0
(total)	12	4	3	1
Total	38	13	3	5

(a): Graft failure due to technical failure, poor graft or rejection; (b): Lymphoproliferative disorders; (c): Myocardial infarction; (d): Hepatoblastoma (4), Cholangiocarcinoma (2), Angiosarcoma (2); *: Died with malignancy

Table 8 Long-term survival

OLT#	Survival (months)	Diagnosis	Comments
3–4 years			
812	36	BD Ca	early cancer in PSC*
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789	37	EHE	
777	38	EHE	
712	39	FL-HCC	size: 4 cm
749	39	HCC	size: 4 cm
603	45	EHE	
4–5 years			
475	54	HCC	size: 2 cm
483	54	HCC	size: 2 cm
> 5 years			
400	61	HCC	size: 2 cm
379	63	HCC	size: 7 cm
351	65	HCC	size: 12 cm
356	65	HCC	size: 2 cm
288	70	HCC	size: 5 cm
316	70	EHE	
231	82	FL-HCC	size: 19 cm
222	88	HCC	size: 2 cm
206	91	HCC	size: 2 cm
198	94	HCC	size: 2 cm
194	95	FL-HCC	size: 15 cm

BD Ca: bile duct cancer, EHE: epithelioid hemangioendothelioma, FL-HCC: fibrolamellar hepatocellular carcinoma, HCC: non-fibrolamellar hepatocellular carcinoma, *PSC: primary sclerosing cholangitis

with hepatocellular carcinoma, but none of 8 patients with fibrolamellar hepatocellular carcinoma developed recurrence within a year after OLT. The differences was statistically significant ($p < 0.0001$).

Among the 62 patients with non-fibrolamellar hepatoma, the tumors of less than 5 cm in the greatest diameter recurred significantly less frequently (2 of 28, or 7%) than those of larger tumors (21 of 34, or 62%) ($p < 0.001$). The number of gross malignant lesions also influenced the recurrence rate: only one (7%) of the 15 single lesions recurred, in contrast to 22 (47%) of 47 multiple lesions ($p < 0.005$). The tumors with gross vascular invasion (8 of 11, or 73%) recurred more frequently than those without gross vascular invasion (15 of 51, or 29%) ($p < 0.05$). The tumors with nodal metastases (3 of 4, or 75%) also recurred more frequently than those without nodal metastasis (20 of 58, or 34%), but the difference was not statistically significant ($p = 0.3035$). Malignant tumors other than hepatocellular carcinoma were too few for analysis.

Main cause of death

Fifty-nine of the 115 patients died during follow-up. The main causes of death are shown in Table 7, together with the time of death and histological diagnosis. The most common cause of death within 3 months after OLT was graft failure due to either technical failure, poor quality of the graft, or rejection. Two patients died with residual malignancy, which, however, was not considered the direct cause of death. No patient died of malignancy during this period. In contrast, the most common cause of death after 3 months was the recurrence of original malignancy (29 of 44, or 66%). These tumor-related deaths contributed to the significantly lower survival of patients with malignancy as compared with that of patients with no malignancy (Fig. 1).

Long-term survivors

A total of 20 patients survived more than 3 years after OLT in the presence of primary liver malignancy (Table 8). Fourteen patients had hepatocellular carcinoma, of whom 3 had fibrolamellar variant, and 9 solitary small (less than 5 cm) lesions. Four of the 20 3-year survivors had epithelioid hemangioendothelioma, and 2 patients had unexpected early bile duct cancer in advanced primary sclerosing cholangitis.

Discussion

The results of total hepatectomy and liver replacement (orthotopic liver transplantation: OLT) for malignancy are mixed (11–16). Although the mere presence of primary hepatic malignancy does not necessarily rule out the possibility of long-term survival, tumor recurrence after OLT is the rule rather than the exception.

Our data presented here indicate that small (less than 5 cm), single lesions of hepatocellular carcinoma with no vascular invasion, developed in advanced cirrhosis, can be very effectively treated by OLT. The long-term survival rates of these patients were as good as those without hepatic malignancy. Among large hepatic malignancies which cannot be resected by subtotal hepatectomy, the fibrolamellar variant of hepatocellular carcinoma and epithelioid hemangioendothelioma showed a favorable prognosis after OLT as compared with other types of primary hepatic malignancy.

However, the results after OLT for large, multiple lesions of non-fibrolamellar hepatocellular carcinoma were quite discouraging, particularly when vascular and/or nodal invasions were present. In these patients tumor recurrence was usually confirmed within a year after OLT, and survival thereafter was limited to several months.

There are three main causes for treatment failures (tumor recurrence), which must be overcome for further improvement. The first cause is an error in the pretransplant evaluation of candidates. Despite a careful search for extrahepatic metastases with CT scan, MRI and various radiographic studies, minute metastatic lesions can easily be missed. The second cause is enhanced tumor growth under immunosuppressive therapy. Tumor doubling time in recurrent hepatocellular carcinoma was measured in 9 of our patients with recurrence in the liver after OLT, and was found to be considerably shortened - 26.2 ± 11.8 days (mean ± SEM) in those patients on cyclosporine-steroid therapy, as compared with the average of 102–195 days without immunosuppression reported in the literature (17–19).

The third cause is a lack of effective anti-cancer therapy following surgical removal of hepatic malignancy. Indeed, many patients remained chemically and radiographically tumor-free for several months after OLT.

This lucid interval provided by total hepatectomy and replacement must be sufficient for some effective

anticancer therapy to eliminate microscopic nests of malignant cells.

It was sometimes tempting to conclude during the review of our experience (11, 15) and that of others (12–14), that liver transplantation for regionally advanced primary malignancy is a futile effort. However, it is a fact that arrest and control of the malignant process over years has been accomplished under some of the least likely circumstances – as with patients who had distant metastasis at the time of transplantation from epithelioid hemangioendothelioma, and patients who had large, multiple lesions of non-fibrolamellar hepatoma. Although some of the histopathological factors influencing the outcome have been identified, many other factors remain to be discovered, and more effective anti-cancer therapy to be developed for liver transplantation to establish a firm role in the treatment of hepatic malignancy.

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