Liver Transplantation for Malignant Disease

Results in 93 Consecutive Patients

JOHN G. O'GRADY,* REX J. POLSON,* KEITH ROLLES,† ROY Y. CALNE,† and ROGER WILLIAMS*

Ninety-three patients with malignant disease underwent orthotopic liver transplantation between May 1968 and April 1987 in the Cambridge/King's College Hospital program. Of 50 patients with primary hepatocellular carcinoma (HCC) (19 with cirrhosis, 31 without cirrhosis, including 7 with fibrolamellar variant), 37 (74%) survived for more than 3 months, and in this group evidence of tumor recurrence was obtained in 24 (64.9%), the longest survivor being 11.8 years post-transplant, and three survived for more than 5 years. Although there is no correlation between the frequency of tumor recurrence and underlying cirrhosis, or histologic type (except fibrolamellar variant), it was observed earlier in those with moderate/poorly differentiated tumors and also when prednisolone and azathioprine was used for immunosuppression. Tumor recurred in all but two of those with peripheral or central cholangiocarcinoma (one alive at 6.1 years) with median survival times of 34 weeks and 56 weeks for the central and peripheral types, respectively. Among the unusual primary tumors, one with epithelioid haemangioendothelioma developed tumor recurrence at 2 years, one of two patients with apudoma is tumor-free at 2.2 years, and the one patient with bile-duct papillary cystadenocarcinoma is alive at 1.7 years. For the secondary hepatic malignancy group, survival times were shorter with little palliation except for two patients with carcinoid syndrome who were free of associated symptoms at 6 and 10 months. Despite the overall high frequency of tumor recurrence in most categories of hepatic malignancy, liver transplantation gave worthwhile survival with a number of patients cured and in the others considerable palliation of symptoms.

From the Liver Unit, King's College Hospital, School of Medicine and Dentistry, London, England, and the Department of Surgery, Addenbrooke's Hospital, Cambridge, England†*

IN THE EARLY DAYS of clinical liver transplantation, primary malignant disease was a favored indication with less difficult surgery and fewer postoperative complications than when transplantation was carried out for advanced cirrhosis. Up until 1979, over 50% of the transplants performed in the Cambridge/King's College Hospital program were for malignant conditions, although it soon became clear that tumor recurrence was all too frequent. Indeed Starzl has written that this form of treatment is conceptually unsound, this view being based on his results in 54 patients with malignant disease transplanted between 1963 and 1985.[1,2] The only patients in that series without frequent early recurrence were those with small hepatomas found incidentally at transplantation carried out for chronic liver disease and the subgroup of patients with the fibrolamellar variant of hepatocellular carcinoma (HCC).[1,2] Although this view has gained some acceptance, other centers including our own and that of Pichlmayr's at Hannover, have continued to transplant patients with malignant disease on the basis that at least in some instances cure is obtained and in others worthwhile palliation.

For the present report we have analyzed the results obtained in a series of 93 consecutive patients with either primary or secondary malignant liver disease treated by transplantation between May 1968, the beginning of the Cambridge/King's College Hospital program, and April 1987.

Materials and Methods

The 93 patients comprised 50 with primary HCC, 26 with either peripheral or central cholangiocarcinoma, nine with unusual primary tumors (five with angiosarcoma or sarcoma, one with epithelioid haemangioendothelioma, two with apudoma, and one with bile-duct papillary cystadenocarcinoma), and 8 with secondary hepatic malignancy including two with the carcinoid syndrome. Of the 50 patients with HCC, 19 had an underlying cirrhosis. The 31 cases arising in a noncirrhotic liver included seven with the fibrolamellar variant (Table 1). There were five patients in the cirrhotic group and three noncirrhotic cases with evidence of hepatitis B virus infection; these included one patient without cirrhosis in whom the only marker was HBV-DNA integration in tumor cells. Four of the patients in the non-

Reprint requests: Roger Williams, Liver Unit, King's College Hospital, Denmark Hill, London SE5 9RS, United Kingdom.

Submitted for publication: November 5, 1987.

TABLE 1. *Data Relating to Groups of Patients Treated with Primary Hepatic Malignancy*

Malignancy	N	Age (yr)		Sex Distribution (M:F)	Interval Between Onset of Symptoms and Transplant
		Median	Range		
Hepatocellular carcinoma					
Cirrhotic	19	50	5–59	15:4	6 mo (3 wk–6 mo)
Noncirrhotic	24	42	10–61	10:14	6 mo (3 wk–9 mo)
Fibrolamellar	7	23	14–51	1:6	5 mo (3–12 mo)
Central cholangiocarcinoma	13	46	16–53	7:6	8 mo (2–24 mo)
Peripheral cholangiocarcinoma	13	49	28–64	7:6	6 mo (4 wk–18 mo)
Bile-duct papillary cystadenocarcinoma	1	36		1:0	2 mo
Primary sarcoma/angiosarcoma	5	32	4–49	2:3	6 mo (3–10 mo)
Epithelioid hemangioendothelioma	1	30		0:1	8 mo
Apudoma	2	34, 36		1:1	2, 4 yr

cirrhotic group had a history of long continued oral contraceptive pill usage.

Six of the cirrhotic patients with HCC had solitary tumors ranging from 2.7 to 6 cm, and 13 had multifocal tumors between 5 and 10 cm in diameter. Tumor masses were generally larger in the noncirrhotic group, and 19 of the 31 cases had a single large lesion of 8–21 cm in diameter, with associated smaller satellite lesions in seven instances. In 12 cases there were multiple masses of between 8 and 15 cm in diameter. Tumor masses in peripheral cholangiocarcinomas were of similar size (8–19 cm in diameter with several discrete masses in six cases); the central cholangiocarcinoma tumors (presenting as biliary obstruction) comprised mainly small scirrhous lesions. Seven of these had been previously treated by surgical insertion of a stent. Two of the cases had a long history of sclerosing cholangitis.

The two patients with apparently primary hepatic apudomas were first diagnosed 2 and 4 years previously and had large tumor masses with increased circulating levels of glucagon/somatostatin and calcitonin/gastrin/pancreatic polypeptide, respectively. The secondary hepatic deposits group included two patients with the carcinoid syndrome and large multiple masses throughout the liver whose symptoms (diarrhea, flushing) were disabling and no longer responded to pharmacologic therapy and repeated hepatic artery embolization. Four patients had earlier resections of a primary tumor elsewhere and in the remaining two cases the extrahepatic primary was removed at the time of transplantation (Table 2).

TABLE 2. *Data Relating to the 8 Patients with Secondary Hepatic Malignancy Treated by Transplantation*

Primary Tumor	Age (yr)	Sex	Resection of Primary
Meningiosarcoma	31	F	4 years previously
Colon	31	F	3 mo previously
Pancreas (tail)	45	F	3 mo previously
Nephroma	54	M	At transplantation
Leiomyosarcoma	57	M	At transplantation
Colon	45	M	11 mo previously
Carcinoid of small bowel	48	M	2 yr previously
Carcinoid of lung	51	F	4 yr previously

In screening for extrahepatic spread, ultrasonographic examination of the upper abdomen, CT scan of thorax and abdomen (replacing whole lung tomography and abdominal lymphangiography used in the earlier patients), and radioisotope bone scanning were carried out routinely. Radiologically demonstrable tumor invasion of a resectable portion of the portal vein was not considered an absolute contraindication to transplantation. In addition, six patients had an exploratory *mini-laparotomy* as part of the transplant workup.

The transplant operation was carried out as described elsewhere.[3] Biliary reconstruction was obtained using predominantly choledochocholedochostomy up to 1975 and thereafter with the biliary conduit technique, except in patients with primary sclerosing cholangitis who had a Roux-en-Y anastomosis.

Sixty-six of the 93 patients had had a previous surgical procedure related to the malignancy (Table 3) including the six patients who had a mini-laparotomy as part of transplantation workup already referred to. In five of these patients a hepatic resection was attempted but not found to be feasible. One of the six patients with previous successful local resection underwent enucleation of a 4-cm HCC from a cirrhotic liver in Japan 2 years prior to transplantation, and there were four cases in the noncirrhotic HCC group who had resections 8 months, 2 years, 3.5 years, and 5.5 years previously, while the final patient had five previous resections spanning a 10-year period.

Statistics

Statistical methods employed include Kaplan-Meier cumulative survival curves, chi square test with Yates correction, and the Mann-Whitney U test.

Results

Primary Hepatocellular Carcinoma

Three-month survival figures were 68.5% for those with an underlying cirrhosis and 77.4% for the noncir-

TABLE 3. *Surgical Procedures Prior to Liver Transplantation*

Diagnosis	No. of Cases	Mini-laparotomy (%)	Exploratory Laparotomy (%)	Attempted Resection (%)	Previous Resection (%)
HCC with cirrhosis	19	2 (10.5)	5 (26.3)	—	—
HCC without cirrhosis	31	3 (9.7)	11 (35.5)	4 (12.9)	5 (16.1)
Central cholangiocarcinoma	13	—	12 (92.3)	—	—
Peripheral cholangiocarcinoma	13	8 (61.5)	1 (7.7)	1 (7.7)	—
Sarcoma/angiosarcoma	5	3 (60)	—	—	—
Other primary tumours	2	1 (50)	—	—	—
Apudoma	2	2 (100)	—	—	—

rhotic group (Fig. 1). Deaths during this early period were due to operative and postoperative hemorrhage (42%), graft failure (25%), sepsis (25%), and chronic rejection (8%). Patients in the noncirrhotic group who had undergone a previous resection or exploratory laparotomy (including mini-laparotomy) had a higher mortality rate (5/20 *vs.* 0/11, $p < 0.05$). There was a similar trend in the cirrhotic patients, but it did not reach statistical significance (3/6 *vs.* 3/13, $p > 0.05$).

After 3 months, the survival curves for the cirrhotic and noncirrhotic groups were also similar with 1- and 2-year survival rates, respectively, of 42.5% and 37.3% as compared to 48.5% and 38.3% (Fig. 1). Tumor recurrence accounted for 59% of the deaths after 3 months, while the remainder were due to sepsis (22.7%) and chronic rejection (9.1%) with single instances of mitozanthrone cardiotoxicity and carotid artery erosion complicating prolonged endotracheal intubation for chronic respiratory failure. Twelve of these patients survived for more than 1 year including two who were free of tumor at the time of death over 5 years post-transplantation. Of the ten patients in this series who are currently alive (as of October 1, 1987), there are five who are more than 1 year post-transplantation, with two of these alive at 4.8 and 11.8 years and free of detectable tumor.

Tumor Recurrence

Tumor recurrence was diagnosed in 24 (64.9%) of 37 patients who survived at least 3 months post-transplantation with no difference between the cirrhotic (69.2%) and noncirrhotic groups (60.0%). Eleven patients were asymptomatic with respect to tumor recurrence at the time this was detected and remained so for a further median period of 6 months (range: 2–13 months). Evidence of recurrence was based on an increase in serum alpha-fetoprotein level (0.7–1.7 years post-transplantation) or appearance of metastases on chest X-ray, ultrasonographic examination, or CT scan (at 3 weeks to 3.3 years) (Fig. 2). The most common clinical signs comprised return of original symptoms (abdominal discomfort, nausea and vomiting, weight loss), pyrexia, skin/buccal mucosa nodules, and pain from skeletal deposits. The principal sites of documented tumor recurrence in the 23 patients were liver (57.9%), lung (57.9%), adrenal (42.1%), bone (26.3%), abdominal cavity (21.1%), and skin (15.8%). In two of four patients with skin metas-

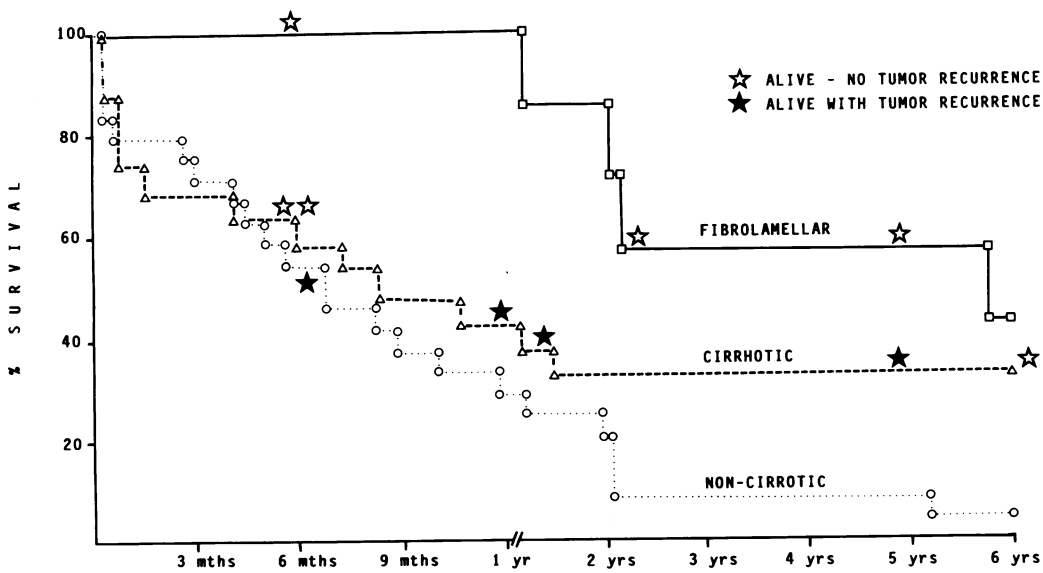

FIG. 1. Kaplan-Meier survival curves for patients transplanted with fibrolamellar HCC and nonfibrolamellar HCC arising in cirrhotic and noncirrhotic livers.

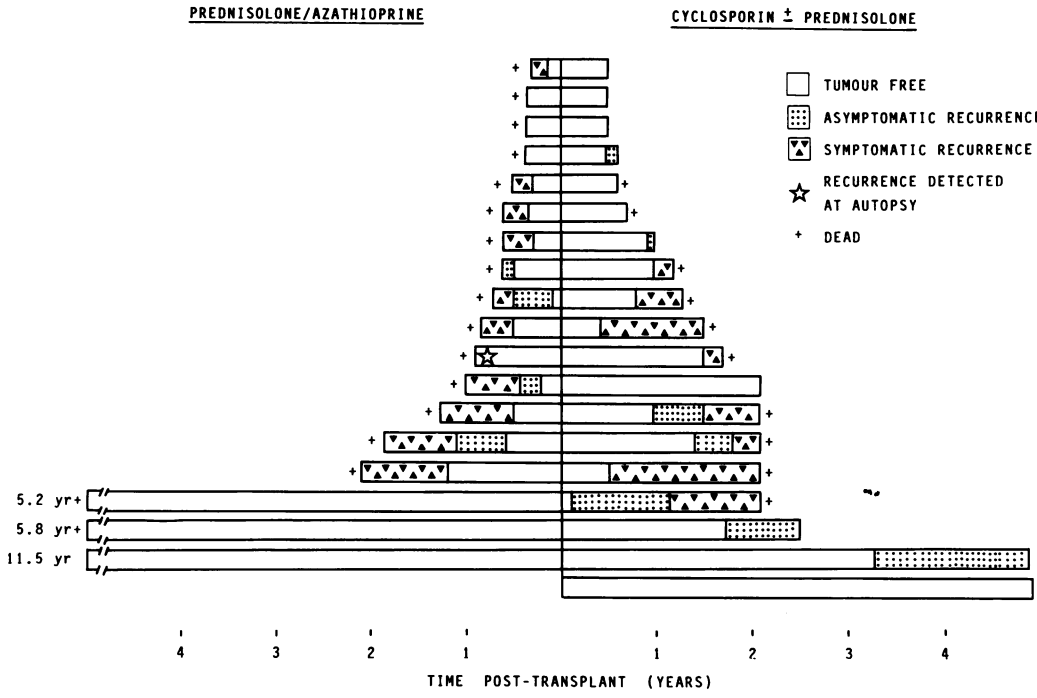

FIG. 2. Overall survival in patients transplanted for HCC and immunosuppressed with prednisolone/azathioprine (1967–1979) or cyclosporine and prednisolone (1980–1987) with breakdown for oncologic-free periods and duration of asymptomatic and symptomatic tumor recurrence.

tases, isolated lesions developed at the site of puncture for a liver biopsy or percutaneous cholangiogram performed prior to transplantation. Ten of the patients who developed recurrence were totally free of symptoms for more than 1 year including one remarkable patient who remains well at 4.8 years with tumor regression on chemotherapy using mitozanthrone and 5-fluorouracil.

Among the seven patients with the fibrolamellar variant of HCC, tumor recurrence was detected in three patients at 6, 9, and 18 months, leading to death at 1.1–2.2 years. Three patients are alive and free of detectable tumor at 3-months, 1.8 years, and 4.5 years, respectively, while the remaining patient was free of tumor when she died 5.8 years post-transplant from sepsis and variceal bleeding complicating the development of cirrhosis (from a transfusion acquired non-A, non-B hepatitis).

The median interval between transplantation and death from recurrence was longer in patients with a well-differentiated tumor on histologic examination than in those with a moderate/poorly differentiated tumor (2 years and 33 weeks, respectively; $p < 0.05$) and all three patients free of detectable malignancy at 2 years had well-differentiated tumors. No correlation was found between tumor size and frequency or rapidity of recurrence, although it is noteworthy that one patient with a 21-cm tumor with multiple smaller lesions was free of tumor at 5.2 years post-transplantation. No correlation was found between tumor recurrence and previous surgery in the noncirrhotic patients surviving more than 3 months (54.5% and 60.0%, respectively), although in the cirrhotic group all three patients who had a previous laparotomy (two exploratory, one mini-laparotomy) developed recurrence as compared to four of ten patients who had not had previous surgery.

Comparison of tumor recurrence rates for the two main immunosuppression regimens used in the program showed no difference between 18 patients maintained on prednisolone/azathioprine and 19 on cyclosporin ± prednisolone (66.7% and 63.2%, respectively), although median survival was longer in the cyclosporin-treated group (9 months and 15 months, respectively; $p < 0.05$). The interval between the time of transplantation and detection of tumor recurrence was also greater in patients on cyclosporin (median: 12 months; range: 3 weeks to 3.3 years) than in the prednisolone/azathioprine group (median: 6 months; range: 4 weeks to 1.2 years; $p < 0.05$). Since nine of the patients on cyclosporin (47.4%) are currently alive as compared to only one in the prednisolone/azathioprine group, it is likely that this difference will become even further accentuated.

Changes in Alpha-fetoprotein

Serial levels for six of the earlier patients have previously been published,[4] indicating a return to within the normal range (<10 ng/mL) in four cases with a half-life of 3–8.5 days. One of these patients continues to have a normal level at 11.8 years, but in the other three patients within 4 months of transplantation the levels had increased again to above the normal range. Since

then there have been a further six cases in whom serum alpha-fetoprotein levels have returned to normal following the transplant. Two of these remain negative at 4–8 months (Fig. 3), and in two patients the level remained in the normal range for at least 10 months before rising again in association with recurrent disease. The sixth patient had only a modest rise in alpha-fetoprotein (31 ng/mL) at 1 year when tumor recurrence was diagnosed.

Cholangiocarcinoma and Other Primary Tumors

Survival curves for both the central and peripheral cholangiocarcinomas are similar (Fig. 4) with 3-month survival rates for both of 53.8%. Sepsis was the major cause of death during this period (81.8%), with hemorrhage (9.1%) and acute graft failure (9.1%) much less frequent. One-year survival rates were also similar for the central and peripheral tumors (30.7% and 38.4%, respectively).

Of the seven patients with central cholangiocarcinoma who survived 3 months, six have documented recurrence of tumor (abdomen five, lung four, bone two, liver one, and skin at operative drain site one) leading to death, a median of 34 weeks post-transplantation. One patient without tumor recurrence who had presented with obstructive jaundice due to a 13-cm cholangiocarcinoma at the hilum is alive and well at 6.5 years. One of the seven patients with peripheral cholangiocarcinoma died at 4 months as a consequence of an intracerebral vascular accident. The other six developed recurrence of tumor (abdomen five, lungs three, liver two, bone two, and cervical lymph nodes one), but the median survival for this subgroup was longer at 1.1 years (range: up to 3.2 years) compared with the central cholangiocarcinoma patients.

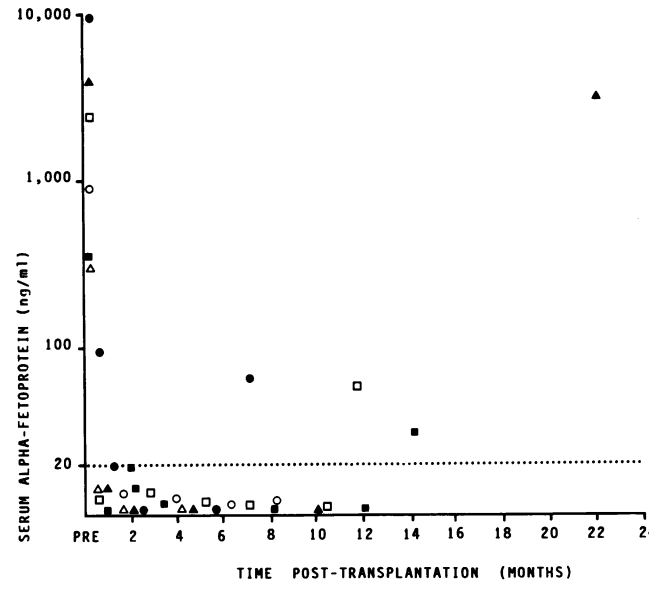

FIG. 3. Serial alpha-fetoprotein levels in six patients with elevated levels pretransplant, which returned to the normal range after surgery.

Four of five patients with primary sarcoma/angiosarcoma died within 7 weeks of surgery as a consequence of hemorrhage or sepsis and the remaining patient has tumor recurrence at 6 months. The single case of epithelioid hemangioendothelioma was in good health for 22 months but then developed rapidly progressive hepatomegaly in association with an apparent microangiopathic hemolytic anemia and impaired renal function, leading to death 2 months later. At autopsy the liver graft was extensively replaced by tumor with no evidence of malignancy elsewhere. The single patient with bile-duct papillary cystadenocarcinoma is alive and free of detectable tumor 20 months after transplantation as

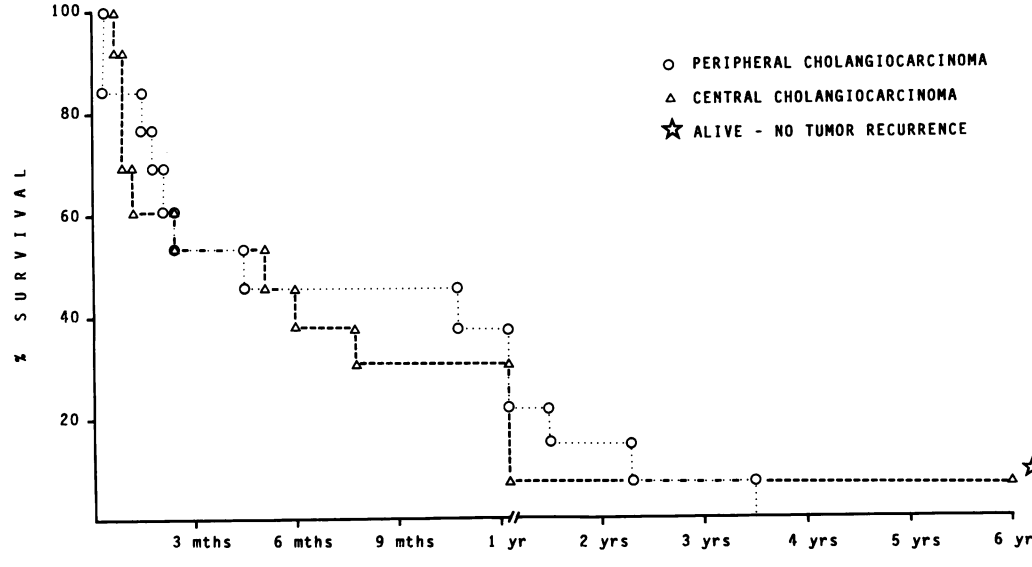

FIG. 4. Kaplan-Meier survival curves for patients transplanted with peripheral and central cholangiocarcinoma.

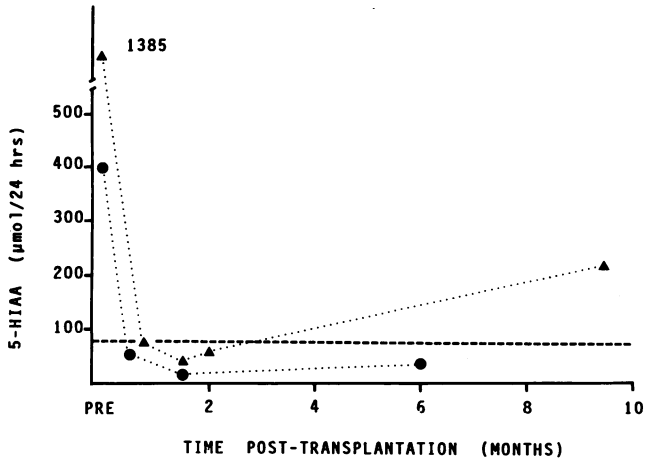

FIG. 5. Urinary excretion of 5-HIAA preliver and postliver transplantation for the carcinoid syndrome.

is one of the two patients with apudomas (2.2 years after transplantation). The other patient with an apudoma had no evidence of recurrence at the time of death from chronic graft rejection (7 months).

Secondary Hepatic Malignancy

Only three of the six patients transplanted for hepatic metastases survived for 3 months, and these died between 22 and 41 weeks from recurrent disease. Of the two patients with the carcinoid syndrome, one died at 7 months with chronic rejection with a normal 5-HIAA excretion; the other is symptom-free at 12 months with no radiologic evidence of tumor recurrence but with increasing levels of 5-HIAA excretion, initially detected at 9.5 months (Fig. 5).

Discussion

The high recurrence rates of primary HCC following transplantation, even in the most recent cases, can only be considered disappointing. Although there have been a number of advances in radiologic techniques for the detection of extrahepatic spread prior to surgery, these are still subject to considerable limitations. Thus, in one recent study of CT scanning, 20–47% of various patient groups had macroscopic tumor nodules at the time of surgery that were not apparent on scanning.[5] It seems reasonable to assume that recurrence of tumor following transplantation is based on microdeposits already present in extrahepatic sites or released during surgical manipulation. Of particular interest was the finding that in cases with a raised alpha-fetoprotein level in serum postoperatively, this could fall to and remain within a normal range for periods of up to 10 months before rising again in association with other evidence of tumor recurrence. Whether adjuvant chemotherapy after transplantation could prolong this interval further or prevent recurrence from developing remains to be established.

The most favorable results reported are those with small asymptomatic tumors found incidentally at the time of transplantation, with 12 of 13 such patients in the Starzl et al. series remaining free of tumor recurrence between 4 months and 15 years (median: 16 months).[1] Most of the cases in the present series that were detected by screening of cirrhotic patients by ultrasonographic examination and alpha-fetoprotein levels had larger tumors than this (>2.7 cm), indicating the need for even more intensive screening of high-risk groups. The recurrence rate in our series with the larger primary HCC tumors was lower at 64.9% than the 77.8% in Starzl's series.[1] In addition, long-term cures were obtained in patients who had not been suitable for hepatic resection because of the localization or extent of tumor or the presence of cirrhosis, and in the remainder considerable palliation was often achieved particularly with well-differentiated tumors and when cyclosporin was used as the main immunosuppressive agent. In several cases subsequent chemotherapy, and in two instances surgical removal of isolated secondary deposits in the adrenal gland, appeared to prolong the period of worthwhile palliation and survival.

The present experience would, however, be in accord with the data of Starzl et al. with respect to the fibrolamellar variant of HCC as the best subgroup, in which 1-year survival was 100% in both series of seven cases each and with overall recurrence rate of 50%.[2] Good results are also obtained with this tumor when local resection is feasible as demonstrated by the study of Soreide et al. of seven patients who survived for between 8 and 41 months with one instance of tumor recurrence during this period.[6]

Whether tumor growth is accelerated by immunosuppression following transplant is difficult to determine. In the present study it is of interest that the rate of growth appears to be slower in patients maintained on cyclosporin, as suggested by the longer median tumor-free interval (12 months) post-transplantation and the longer lag period before the reappearance of alpha-fetoprotein in serum. In the study by Iwatsuki et al.[1] the median interval between transplantation and HCC was only 4 months, but many of these patients were probably treated in the precyclosporin era. The possible acceleration of tumor growth by immunosuppressive therapy was one of the factors prompting the conclusion of Iwatsuki et al. that transplantation for malignant disease was conceptually unsound.[1] We believe this conclusion needs to be reconsidered with greater dependence on cyclosporin, especially since a median oncologically free interval of 1 year provides a good basis for worthwhile palliation.

The chances of a potentially curative resection of central (bile-duct) cholangiocarcinoma being possible are small, as indicated in the study by Blumgart et al. in which only 18 of 94 patients with hilar cholangiocarcinoma were treated in this way, and these had a mean survival of 17 months.[7] A greater percentage of such patients are amenable to treatment by transplantation, and our 3-month survival rate of 53.8% is similar to the 50% achieved by Iwatsuki et al.[1] However, only two patients in both studies have remained free of tumor. No patient with peripheral cholangiocarcinoma has to date been cured of tumor, although a median survival of 1.1 years with a range of up to 3.5 years represents worthwhile palliation. Poor results with primary angiosarcoma/sarcoma are not surprising, but the recently recognized variant, epithelioid hemangioendothelioma, with a much less aggressive natural history remains a worthwhile category.

Patients with apudomas and secondary carcinoid tumors constitute a special group with respect to liver transplantation. Not only is tumor growth naturally slow with these tumors, but the dramatic relief of associated symptoms obtained with a successful graft, particularly the disabling carcinoid syndrome, is a remarkable event to witness.

Our results do little to support the use of transplantation for patients with secondary hepatic malignancy (excluding carcinoid). Pichlmayr et al., however, considered the palliation conferred by transplantation to be valuable despite the short period of survival.[8] The most encouraging data comes from the Vienna group who reported a 70% 1-year survival in ten patients, with one patient free of detectable tumor at 3 years.[9] There is also a single patient in the UCLA series with metastatic gastric leiomyosarcoma who is alive and free of detectable tumor 21 months post-transplantation.[10] At least some categories of patients within this group probably merit reconsideration with regard to transplantation, especially those with hepatic metastases for a primary colonic carcinoma resected some years previously.

References

1. Iwatsuki S, Gordon RD, Shaw BW, Starzl TE. Role of liver transplantation in cancer therapy. Ann Surg 1985; 202:401–407.
2. Starzl TE, Iwatsuki S, Shaw BW, et al. Treatment of fibrolamellar hepatoma with partial or total hepatectomy and transplantation of the liver. Surg Gynecol Obstet 1986; 162:145–148.
3. Calne RY. Recipient operation. *In* Calne RY, ed. Liver Transplantation. Philadelphia: Grune & Stratton 1983; 155–174.
4. Johnson PJ, Williams R. Serum alpha-fetoprotein estimations and doubling time in hepatocellular carcinoma: influence of therapy and possible value in early detection. JNCI 1980; 64:1329–1332.
5. Mittal R, Kowal C, Starzl TE, et al. Accuracy of computerised tomography in determining hepatic tumor size in patients receiving liver transplantation or resection. J Clin Oncol 1984; 2:637–642.
6. Soreide O, Czerniak A, Blumgart LH. Large hepatocellular cancers: hepatic resection or liver transplantation. Br Med J 1985; 291:853–857.
7. Blumgart LH, Benjamin IS, Hadjis NJ, Beazley R. Surgical approached to cholangiocarcinoma at confluence of hepatic ducts. Lancet 1984; 1:66–70.
8. Pichlmayr R, Brolsch C, Wonigeit K. Experience with liver transplantation in Hannover. Hepatology 1984; 4:56S–60S.
9. Mulbacher F, Piza F. Orthotopic liver transplantation for secondary malignancies of the liver. Transplant Proc 1987; 19:2396–2398.
10. Colonna JO, Ray RA, Goldstein LI, et al. Orthotopic liver transplantation for hepatobiliary malignancy. Transplantation 1986; 42:561–562.