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Liver Transplantation For Malignant Tumors

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According to the National Cancer Institute's statistics, 13,600 new cases of malignant tumors of the liver and biliary passages were expected to occur in 1986 in the United States.[4] The optimal treatment for malignant liver tumors is partial or subtotal resection of the liver. These days resection can be done with a low mortality.[12] The resectability rates reported vary from 5 per cent to 30 per cent in different series.[5] Conceptually, total hepatectomy followed by orthotopic liver transplantation would be the only possible surgical method of cure if the tumor was too extensive to be resected without a total hepatectomy while still being confined solely to the liver. The same situation applies if a conventional resection was to be precluded by coexisting cirrhosis.

In the initial development of liver transplantation as a clinical procedure, extensive hepatic tumors were thought to be an ideal indication. Thus, the second recipient of an orthotopic liver transplantation was an individual with a hepatoma in a cirrhotic liver. The first relatively long-term survivor of a liver transplant was an individual with a hepatoma who died 13 months after transplantation due to tumor recurrence.[17] As the experience with liver transplantation increased and as the followup of patients transplanted for malignant tumors grew, it became quite clear that the results of transplantation for hepatic malignancy were not as good as initially expected.[22] With the use of cyclosporine (CyA), liver transplantation results improved dramatically.[21] Figure 1 shows the cumulative survival curve for 930 consecutively transplanted patients and a second curve for the 70 patients with malignant tumors who were transplanted using CyA as the major immunosuppressive agent.[18] Even though the early postoper-

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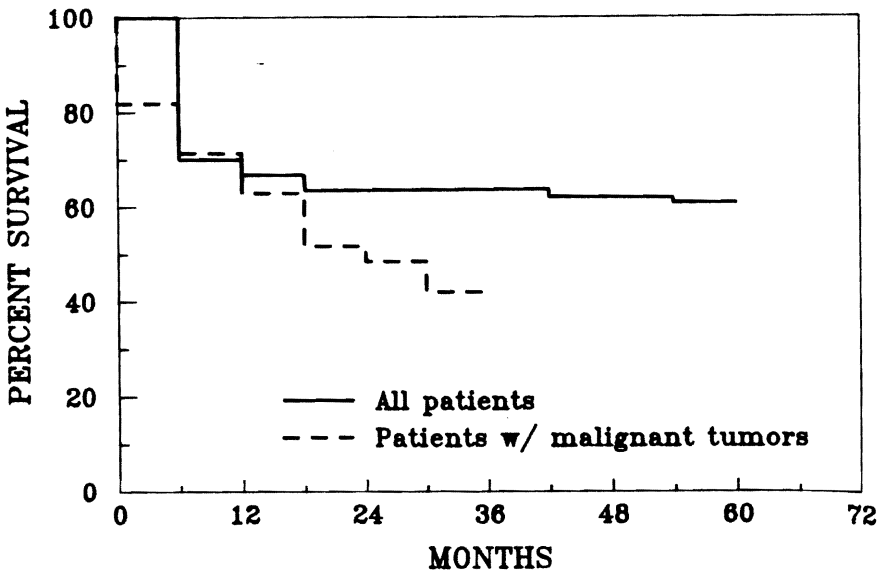

Figure 1. Cumulative survival of all 830 recipients with all diagnoses compared with 70 recipients with malignant tumors transplanted during CyA era.

ative death rates were similar for the two groups, the recipients transplanted for hepatic malignancy have been plagued by clinically evident recurrences of their tumors, which have frequently resulted in the death of the recipient. As a result of this experience, a serious question remains: Do the results achieved justify continued efforts at treating malignant diseases of the liver with transplantation?

In the combined Denver-Pittsburgh experience, during the precyclosporine era, 13.5 per cent of recipients had hepatic malignancy as the indication for liver transplantation compared to a figure of 5.6 per cent during the cyclosporine era. In contrast to this American experience, malignant tumors of the liver have consistently been a larger fraction of the total European experience. In the recent report of the European liver transplant registry, individuals with malignant tumors comprised 29.14 per cent of the total experience.[3] In the individual series of the Hannover group, tumor has been the principal indication in 33.8 per cent of the cases.[10] Despite the greater experience with tumor as an indication for transplantation, the overall European results have been equally as disappointing as the American experience with this particular indication.

There are, however, some rays of hope. For example, patients with incidentally discovered hepatomas in their hepatectomy specimen having been removed for some other indication have uniformly done well. Moreover, patients with certain histological types of hepatic malignancies have had better survivals than have others.

In this article we will present data on 70 patients (Table 1) (adults and children) with either primary malignant or metastatic tumors, who were treated by orthotopic liver transplantation during the cyclosporine era at the University of Colorado Health Sciences Center (1980), at the University

Table 1. *Histology of Malignant Liver Tumors Treated by Orthotopic Liver Transplantation During the Cyclosporine Era*

Primary		64
Hepatoma		43
Hepatocellular	34	
Fibrolamellar	9	
Bile duct cancer		11*
Epithelioid hemangioendothelioma		6
Miscellaneous (angiosarcoma 1, cholangiocarcinoma 1; unclassified 2)		4
Metastatic		7
Neuroendocrine tumors		5*
Leiomyosarcoma		1
Adenocarcinoma of unknown origin		1
TOTAL		**70**

*One patient was transplanted for metastatic carcinoid tumors. A bile duct cancer was detected in the hepatectomy specimen.

of Pittsburgh (1981–July 1987), or the University of Pittsburgh's affiliate program at Baylor University Medical Center in Dallas (April 1985–July 1987).

EVALUATION AND SELECTION OF CANDIDATES

Clearly, not all patients with primary hepatic malignancies unresectable by conventional means are candidates for total hepatectomy and orthotopic liver transplantation. In general the presence of distant metastases is an absolute contraindication for liver transplantation except for a very few select histological types (fibrolamellar variant of hepatocellular carcinoma and epithelioid hemangioendothelioma) of tumor; thus it is necessary to evaluate each of these potential candidates for the presence of extrahepatic disease.

Overt intraabdominal spread is usually ruled out by reviewing previous operative records and a CT scan of the abdomen. The presence of pulmonary metastases is evaluated by routine chest roentgenograms and a full chest CT scan. Intracranial tumor spread is evaluated by either a CT scan or a nuclear magnetic resonance image (MRI) of the head. The possibility of skeletal metastases is investigated with a bone scan. Frequently degenerative disease of the spine and old traumatic lesions, particularly of the ribs, can cause confusion. A bone biopsy should be obtained in such instances from the suspicious site. Using the above methods, combined with a thorough abdominal exploration, the presence of metastatic disease can almost always be detected either prior to or at the time of transplantation. However, micrometastases are still frequently not detectable with current methods and continue to be responsible for posttransplant recurrences and recipient death.

Quite often a final decision regarding transplantation is not possible until the patient has had an abdominal exploration once a suitable organ becomes available. At this point the intraabdominal extent of the disease and presence of another primary tumor could be assessed.

Occasionally individuals who are transplanted for an indication other than malignancy are found to have a coincidental malignancy in their hepatectomy specimen. Typically these patients have been evaluated as is any other individual with endstage liver disease when the unrecognized malignancy has not played a role in the pretransplant decision-making process.

In patients with sclerosing cholangitis, an attempt should be made to obtain brushings of the biliary tree (percutaneous transhepatic or endoscopic retrograde route) for cytologic evaluation, because bile duct cancer is frequently found in such cases. Moreover, clinically it is sometimes quite difficult to distinguish between primary sclerosing cholangitis and bile duct carcinoma, particularly in patients without a history of inflammatory bowel disease and a relatively short history of cholestatic liver disease. Despite these precautions, patients with primary sclerosing cholangitis stand a 10 per cent chance of having a coincidental bile duct carcinoma in their hepatectomy specimen.[14]

SURGICAL TECHNIQUE

(see also "Surgical Technique of Orthotopic Liver Transplantation)

When liver transplantation is performed for a malignant liver tumor, certain modifications of the usual transplant procedure are utilized.[19] In all such cases, another patient is used as a "back-up" candidate so that if the pretransplant abdominal exploration and dissection reveal extrahepatic extension, the transplant can be discontinued and the donor liver is transplanted into the "back-up" candidate rather than being wasted.

Although the preoperative screening procedures used to detect extrahepatic tumor spread are relatively accurate, a careful assessment of the abdomen of all such recipients for the spread of the tumor should be made at each such potential transplant procedure to determine that the tumor is confined only to the liver. The hilar structures are carefully assessed for tumor thrombi in vessels and hilar lymph nodes. Any suspicious looking tissue (omentum, lymph nodes, and peritoneal nodules) is examined by frozen section. All of the hilar, paraduodenal, and suprapancreatic lymph nodes are removed with the hepatectomy specimen. The hepatectomy specimen should include a wide excision of the gastrohepatic ligament, the hepatoduodenal ligament, and a skeletonization of the vascular structures away from the hilum. Any structure attached to the liver (diaphragm and omentum) in the area of the tumor is also excised. The common bile duct should be transected distally behind the duodenum, and a Roux-en-Y choledochojejunostomy is the preferred method of subsequent biliary drainage of the allograft.

It is important to be sure that any tumor in the liver is primary, and not a metastatic tumor arising in some other abdominal organ. In very rare cases a metastatic tumor coexisting with a primary tumor will be detected either during the evaluation procedures or during the "transplant" exploration. If a decision is made to proceed with the transplant, the primary tumor should be resected prior to the hepatectomy in order to avoid any

Table 2. *Indication for Transplantation in Patients with Endstage Liver Disease Secondary to Noncancerous Etiologies*

Cirrhosis	6
Tyrosinemia	3
Biliary atresia	2
Alpha-1-antitrypsin deficiency	1
Familial cholestasis	1
Neville's disease	1
Total	14

spread of tumor cells to the allograft while the tumor is being excised (see also section on metastatic tumors, page 189).

HEPATOCELLULAR CARCINOMA (NONFIBROLAMELLAR)

This is the most common form of primary liver malignancy. It is more common in the Far East, where a high percentage of such patients are positive for hepatitis B virus. A large percentage of these tumors are unresectable by conventional means when they are first diagnosed. As a result, total hepatectomy followed by orthotopic liver transplantation is the only possible surgical form of therapy. A very high rate of posttransplant recurrences plagues these patients and adversely affects their long-term survival.

Thirty-four patients with hepatocellular carcinoma have been transplanted by us in the cyclosporine era. These cases can be divided into two groups based on the indication for transplantation. Group 1 comprises 14 patients in whom the indication for transplant was endstage liver disease secondary to any of a multitude of noncancerous etiologies. Each of these had an incidental hepatocellular carcinoma. The indications for transplantation in these cases are itemized in Table 2.

Their ages ranged from 3 to 53 years with the average being 26 years. Only 4 were males. All survived the perioperative period. Seven had two or more malignant lesions in their hepatectomy specimen. The tumors varied in size from 0.5 cm to 7.0 cm in diameter. None of these 14 had any lymph node involvement.

Only 1 of these 14 cases has had a recurrence. This single patient had recurrence in the lumbar spine 17 months following transplantation and died 6 months later (OT No. 344). Initially he was thought to have disseminated small cell cancer of the lung and was reported as such in a previous publication from our center. At autopsy he had involvement of liver allograft, lungs, lumbosacral spine, and ribs. Review of the autopsy material by three independent pathology groups has confirmed the disease as being a recurrence of the hepatocellular carcinoma. He had multifocal, well-differentiated hepatocellular carcinoma (largest tumor nodule 3.5 cm in diameter) in the original hepatectomy specimen. Still unclear is what factors contributed to the unbridled nature of his tumor compared to that of the others in this group.

The remaining 13 patients in this group are alive and free of disease

with followups ranging from 3 to 73 months; 6 of the 13 have survived beyond 3 years. The longest surviving patient had a poorly differentiated hepatocellular carcinoma (2.5 cm in diameter) that arose in a setting of cirrhosis caused by alpha-1-antitrypsin deficiency.

In Group 2 were 20 patients who received their liver transplants with hepatocellular carcinoma as the indication. Two had had a previous hepatic resection (1 week and 12 years earlier). Eleven were males. The average age of this group was 37.5 years (range 11–58 years); 9 had other associated hepatic diseases (7 postnecrotic cirrhosis, 2 tyrosinemia), and 5 had evidence of hepatitis B infection.

Extent of Disease

All 20 had disease confined solely to the liver based upon their pretransplant evaluations. At laparotomy, only one had disease extending on to the diaphragm and abdominal wall.

Early Deaths

Five of these twenty individuals died within 2 months following their transplants as a result of some early postoperative complication. Four of these had autopsies, and no residual tumor was found in any of them. Thus, the pretransplant and intraoperative evaluation procedures utilized in these cases appear to have been relatively accurate in detecting extrahepatic disease.

Recurrence

Fifteen of these twenty patients survived for periods greater than 2 months and were evaluated for the presence of disease recurrence and long-term survival following transplantation. Eight of these 15 developed a disease recurrence at intervals of 4 to 12 months following their transplant. One of these patients died of a myocardial infarction at 14 months with a suspected recurrence in his ribs. Unfortunately no autopsy was obtained. In cases where recurrences have been seen, the allograft liver was the first site for the recurrence in four; the lungs were the first site of recurrence in three; the skeleton was the site in 1. Ultimately many other organs were involved in each such case.

Late Deaths

Six of the eight patients with known recurrences and another with suspected recurrence died one to eight months following the first evidence of their recurrence. All the recurrences seem to occur within the first year following transplantation. Six of the total of twenty patients transplanted for hepatoma are alive with no evidence of disease 54, 44, 11, 10, 8, and 6 months after transplantation. Whether the 2 patients surviving 54 and 44 months are "cured" of their tumor remains to be seen but seems likely. It is interesting that each of these 2 patients had a hepatic resection prior to the transplant. The patient surviving 54 months developed fulminant hepatic failure following his original resection and was transplanted 1 week later. The other had had his hepatic resection 12 years previously and required a total hepatectomy as his second procedure because of extensive recurrence in both lobes.

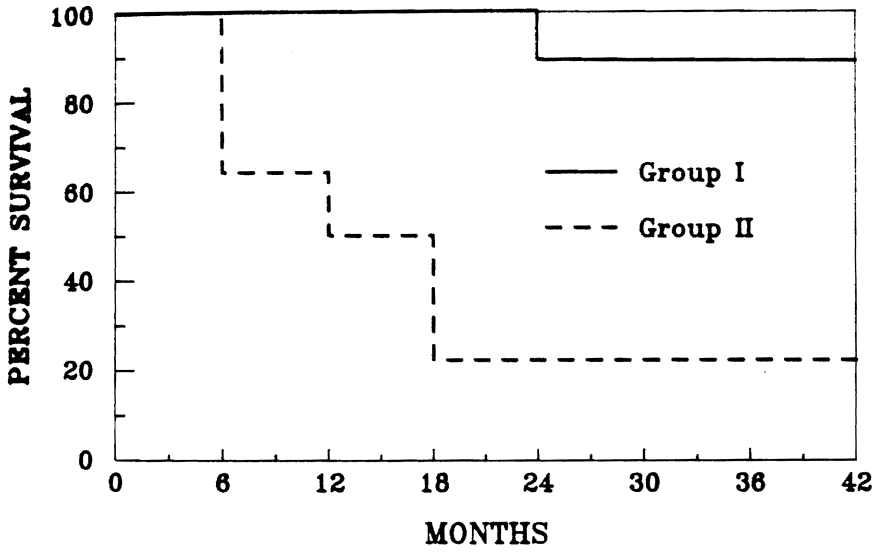

Figure 2. Cumulative survival of patients with hepatocellular carcinoma during CyA era.

In the report from the European Liver Transplant Registry, patients with hepatocellular carcinoma (unstratified) have had a 30 per cent 2-year actuarial survival.[3] In the data compiled by Pichlmayr from 7 European centers, 30.5 per cent (48/157) of such patients have survived 1 year or more, and 17.1 per cent (27/157) have survived for more than 2 years. Pichlmayr found survival to be poorer in patients with associated cirrhosis. Lymph node involvement had a severe negative impact on survival.[10] The survival of our patients with hepatocellular carcinoma is shown in Figure 2. The Group I patients who had an incidental carcinoma did extremely well with a single exception (actuarial survival at 2 years, 88 per cent). Some of these individuals had relatively large tumors that were poorly differentiated histologically. In contrast, the Group II patients who received transplants for unresectable tumors did considerably poorer and several have died as a result of their recurrent disease (actuarial survival at 19 months is 22 per cent). These cases clearly document the fact that undetectable micrometastases remain even after a total hepatectomy and, when present, lead to an early recurrence and eventual death. Immunosuppression, a necessity following organ transplantation, creates an environment conducive to tumor growth.

The situations with hepatocellular carcinoma and breast cancer appear to be similar: Survival in breast cancer has been improved by identifying those patients at high risk for harboring micrometastases and administering adjuvant therapy (chemo- and hormonal therapy) to them. The application of this strategy following liver transplantation has been hampered by a lack of any effective chemotherapeutic agents against hepatocellular carcinoma and the fear of the added immunosuppression and leucopenia that these agents produce.

FIBROLAMELLAR HEPATOCELLULAR CARCINOMA

"Fibrolamellar" carcinoma of the liver, a hepatocellular carcinoma with a favorable prognosis, has been recognized as a definite clinicopathological entity since 1980. The unique histologic features and clinical behavior of the tumor have been described in detail only recently by the reports of Craig and colleagues[6] and Berman and coworkers.[2] This tumor usually occurs in young adults or adolescents (mean age 23.2 years) with a male to female ratio of 1:2. The distinctive histological feature of this tumor is its polygonal cells with an abundant eosinophilic cytoplasm and uniformly large oval and vesicular nuclei. The fibrous stroma of this tumor is composed of fibrillar bands of collagen that are arranged in a lamellar manner between groups of tumor cells. The stroma is usually dense at the periphery and forms either a capsule or pseudocapsule. Cirrhosis does not appear to occur at an increased rate in individuals with this subgroup of hepatocellular cancer. Typically, these tumors grow slower, have a higher resectability rate, and a longer survival rate than do other types of hepatocellular carcinoma.[6, 20]

Nine patients with this particular variant of hepatocellular carcinoma have been treated by us using total hepatectomy and orthotopic liver transplantation in the CyA era. The average age at the time of transplantation for this group was 36.1 years and interestingly, seven were males. In only one of these nine was the tumor discovered incidentally following a transplant for postnecrotic cirrhosis (OT 712). A clinical summary of these nine patients is given in Table 3.

Extent of Tumor

None of nine individuals with fibrolamellar carcinoma had any known distant metastases at the time of the transplant. In two of the nine (OT 231, OT 621) the tumor was found to be infiltrating the diaphragm and required excision of a portion of the diaphragm along with the liver. In 3 (OT 194, OT 338, and OT 970), varying degrees of vascular invasion were evident upon histologic examination.

Survival

Three of these 9 cases have died of a nontumor-related cause 1, 7, and 32 months later. All 3 of these cases had had a serious problem with their allograft function and required retransplantation. In the two cases that were autopsied, no evidence of recurrent tumor was found, though one had coincidental adenosquamous carcinoma of the lung. Of the remaining six patients, two have died as a direct consequence of recurrent disease 32 and 33 months later. The other four are alive, but one has recurrent disease. The mean survival for this group has been 30.3 months.

Recurrence

Three patients transplanted for fibrolamellar carcinoma manifested recurrent disease. In one case, the recurrence took place solely in the lungs. This patient has had multiple pulmonary resections and was given a course of adjunctive chemotherapy. She is currently alive and working full

Table 3. *Clinical Characteristics and Results in 9 Patients Following Liver Transplantation for Fibrolamellar Hepatocellular Carcinoma*

PATIENT	AGE	SEX	ASSOCIATED LIVER DISEASE	TIMING AND LOCATION OF FIRST RECURRENCE	TREATMENT FOR RECURRENCE	ORGANS ULTIMATELY INVOLVED BY RECURRENCE	SURVIVAL	MAIN CAUSE OF DEATH
OT 172	24	M	—	20 mo, pelvis	None	Pelvis, rectum, bladder, peritoneal carcinomatosis	Died/33 mo	Carcinomatosis
OT 194	26	M	—	None	—	—	Alive/74 mo	
OT 231	23	F	S/P right hepatic lobectomy 5 years	13 mo, lungs	Multiple pulmonary resections plus chemotherapy	Lungs	Alive/65 mo	
OT 300	25	M	—	None	—	—	Died/32 mo	Required retransplantation × 2 for hepatic artery and biliary problems, autopsy showed no recurrence
OT 338	25	M	—	16 mo liver, lungs	Chemotherapy	Liver, lungs, peritoneal carcinomatosis	Died/32 mo	Extensive carcinomatosis
OT 466	48	F	—	None	Adjuvant chemotherapy	—	Died/7 mo	Required retransplantation × 2 for rejection and primary non function
OT 621	46	M	Hepatic failure S/P right trisegmentectomy 1 week	—	—	—	Died/1 mo	Autopsy showed no residual disease, an incidental adenosquamous CA of lung was seen
OT 712	42	M	Postnecrotic cirrhosis	—	—	—	Alive/20 mo	
OT 970	65	M	Hemochromatosis	—	—	—	Alive/10 mo	

time, 52 months following her initial recurrence. The second case had a recurrence in the lungs and allograft liver as well as extensive peritoneal implants. In the third, the recurrence was confined to the abdomen.

There is no specific mention of this particular variant of hepatocellular carcinoma in the reported European series.[10] When these patients are grouped with those with more usual types of hepatocellular carcinoma, the survival of the entire group appears spuriously better.

It is of some interest that a limited number of distant metastases may not be a contraindication to transplantation for patients with this particular subgroup of hepatocellular carcinoma. Moreover, it appears as if recurrent disease should be aggressively treated either by resectional surgery or resection combined with chemotherapy.

BILE DUCT CARCINOMA

Bile duct cancers have been an identifiable fraction (15.5 per cent) of the cases that have been transplanted in our series. On the average, these patients have been older than other patients with malignancy as the indication for transplantation (43.8 years versus 37.5 years for patients with hepatocellular carcinoma).

Of the 11 cases in this series, 3 had tumors isolated to their major bile ducts. One of these has actually been transplanted for multiple hepatic metastases arising from a small bowel carcinoid. A bile duct cancer was found unexpectedly in the hepatectomy specimen. Eight of the cases developed their bile duct adenocarcinoma in association with sclerosing cholangitis. The course of these patients is shown in Table 4.

Sclerosing Cholangitis and Bile Duct Carcinoma

In six of the eight cases found in association with sclerosing cholangitis, the tumor was unsuspected and discovered incidentally within the hepatectomy specimen. In fact in one of them the tumor was missed on the initial histological examination of the hepatectomy specimen and was discovered only 6 months later during a review of the material. One of the remaining two patients with a bile duct tumor was suspected to have a tumor before the transplant, but a specific histological diagnosis could not be established prior to transplantation, and no gross tumor was found at the time of the transplant procedure. In the other patient a gross tumor was evident in the hepatic hilum and lymph nodes at the time of the transplant.

Among the 55 patients with sclerosing cholangitis transplanted by our group, six (11 per cent) had adenocarcinoma of the bile ducts. The duration of sclerosing cholangitis (PSC) in those with and without bile duct cancers was similar.[14] This finding underscores the need for aggressive diagnostic procedures, including PTC and ERCP with brush biopsies of the bile ducts in the pretransplant evaluation of all patients with sclerosing cholangitis.

Early Deaths

Two patients transplanted for bile duct cancer died in the early postoperative period (4 and 22 days) from complications related to graft

Table 4. *Clinical Characteristics and Results in 11 Patients Following Liver Transplantation for Bile Duct Carcinoma*

TIMING AND

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PATIENT	AGE	SEX	ASSOCIATED LIVER DISEASE	TIMING AND LOCATION OF FIRST RECURRENCE	TREATMENT FOR RECURRENCE	ORGANS ULTIMATELY INVOLVED BY RECURRENCE	SURVIVAL	MAIN CAUSE OF DEATH
OT 176	33	F	PSC UC	10 mo, right lobe of the liver Roux loop of jejunum	Radiation therapy to porta hepatis and liver	Liver, intestine	Died/12 mo	Carcinomatosis
OT 185	58	M	—	—	—	—	Died/1 mo	Liver failure and sepsis, autopsy: no evidence of recurrence
OT 200	27	M	—	5 mo, abdominal wall	Radiation therapy	Liver, mesenteric lymph nodes	Died/9 mo	Carcinomatosis
OT 623	47	F	PSC	14 mo, liver	Irradiation, chemotherapy	Liver, skull, clavicle	Died/17 mo	No autopsy
OT 675	35	F	PSC	—	—	Lymph nodes at porta hepatis—splenic capsule omentum—pelvic peritoneum-both ovaries	Died/4 mo	Staphylococcal sepsis
OT 812	24	M	PSC	—	—	—	Alive/15 mo	—
OT 813	38	M	PSC UC	—	—	—	Alive/15 mo	—
OT 825	58	M	PSC UC cholangiocarcinoma detected 6 mo later	Biliary anastomosis 11 mo/peritoneal carcinomatosis	Intraductal iridium	Liver, hepatic artery, anastomosis, peritoneum, intestines	Died/13 mo	Extensive carcinomatosis
OT 888	59	M	PSC	12 mo clavicle	Radiation therapy	—	Alive/13 mo	—
OT 953	41	M	Carcinoid of small bowel with liver metastases (incidental cholangiocarcinoma)	3 mo/omentum	—	—	Died/5 mo	Extensive carcinomatosis
OT 982	61	M	PSC UC	—	—	—	Died/0 mo	—

PSC: Primary Sclerosis Cholangitis
UC: Ulcerative Colitis

failure and sepsis. One of these two had an autopsy, and no residual disease was detected. A third died 4 months following the transplant. At autopsy, extensive recurrence in the abdominal lymph nodes, omentum, and pelvic peritoneum was found. This individual was the patient who had gross extrahepatic disease evident at the time of the original transplant procedure. Seven out of the nine recipients who survived the early postoperative period have been treated with adjuvant upper abdominal radiation therapy. One of them also received adjuvant chemotherapy with 5-fluorouracil.

Recurrences

Among these nine patients who survived the initial postoperative period, seven developed a recurrence at an average of 8.5 months following transplantation. Invariably tumor recurrence has had a disastrous consequence. Six of them died within 5 months of the detection of their recurrence.

The majority of recurrences occurred in the abdominal cavity, particularly within the hepatic allograft. One had distant metastases to the clavicle.

Only two cases are alive without evidence of recurrent disease and good allograft function 15 months posttransplant. The experience of the Cambridge group has also been disappointing with regard to this subgroup of cases. None of their eight patients with bile duct carcinoma has survived more than 1 year.[16] The small number of total cases makes it impossible to determine the impact of any specific histopathological feature on subsequent survival with the exception that the presence of lymph node metastases, perineural invasion, and residual tumor at a surgical margin have an adverse affect upon survival. In our experience four individuals had residual tumor at the margins of their resection, four had perineural invasion, and two had lymph node metastases. Consistent with our experience, Pichlmayr has reported a strong influence of the status of lymph nodes upon subsequent survival. Specifically those with positive lymph nodes had dismal survival rates of 13 per cent at 1 year and 0 per cent at 2 years. In contrast, those with negative lymph nodes had a 100 per cent survival at 1 year and an 83 per cent survival at 2 years.[10] Whether these results will continue in other series and with a period of longer followup remains to be determined.

EPITHELIOID HEMANGIOENDOTHELIOMA

Epithelioid hemangioendothelioma is a relatively recently characterized malignant tumor of the liver.[23] The cell of origin of this tumor is an endothelial cell, thus this tumor can occur in any part of the body, not just the liver.[23] Nonetheless, occasionally it occurs in the liver as a primary tumor. It typically grows slowly but aggressively with the natural history of the disease spanning 5 to 10 years. Metastases most often occur to bones, lymph nodes, and pleura.

Factor VIII-related antigen is demonstrable by immunoperoxidase staining in the cytoplasm of these tumors, and it acts as a specific tumor marker.[24] These tumors are often multiple and located in both lobes.

precluding curative resection without a total hepatectomy. In such cases liver transplantation is the only option available. In our series, six transplants have been performed for this type of tumor, comprising 8.5 per cent of all of the malignant tumors that were treated by liver transplantation. The patients' ages ranged from 24.8 to 37.9 years with a mean of 30.8 years. Fifty per cent were males. Two had known distant metastases (one to lung and one to rib) and four had extrahepatic intraabdominal disease (3 in lymph nodes and 1 in diaphragm) at the time of their transplant.

Survival and Recurrences

All six patients with hemangioendothelioma as the indication for transplantation survived the procedure and are currently alive without evidence of recurrence with one exception. This patient had a recurrence in the upper lobe of a lung and mediastinum 21 months following transplantation. The two individuals with distant metastases prior to their transplant have remained stable with no progression of the disease.

Hepatic allograft function has been good in each case with a followup ranging from 10 to 49 months and a mean survival of 22.3 months to date. Four patients have been given adjuvant chemotherapy with adriamycin postoperatively. The longest survivor (49 months) did not receive any chemotherapy postoperatively and had tumor involving the diaphragm.

Because the natural history of this disease is long, it is too early to predict the ultimate outcome with transplantation in this particular group of patients. Ishak and colleagues have reported 32 patients with this type of liver tumor and found that these patients survive for long periods without any treatment.[11] Whether regional lymph node involvement imposes an additional risk in terms of tumor recurrence remains to be determined. The role of posttransplant adjuvant chemotherapy in these cases also is yet to be defined. The fact remains that in these patients, the presence of a limited number of distant metastases, as is the case with fibrolamellar hepatocellular carcinoma, is not a contraindication to transplantation.

METASTATIC TUMORS OF THE LIVER

The liver is the organ that is most frequently involved with metastases from tumors arising elsewhere in the body. In the past, the presence of hepatic metastases has been considered to be evidence of incurability. In recent years, however, there has been a growing interest in hepatic resections as a treatment for certain isolated metastatic lesions, particularly those arising from the colon. Long-term survival results following resection of such isolated hepatic metastases of colorectal cancer have been reported by several different authors.[1, 7] Liver resection is impossible when the entire organ is studded with metastases.

In such patients, total hepatectomy with orthotopic transplant is the only hope for a surgical cure. Currently European centers have the greatest experience with this group of patients,[3, 10] in which colorectal metastatic tumors are the largest subgroup. Patient survival has been poor in most instances.

In our series, we treated seven patients with metastatic cancer to the liver by total hepatectomy and orthotopic transplantation. This group includes three men and four women, whose ages range from 35 to 54 years. Five had metastatic neuroendocrine tumors (carcinoid in two, glucagonoma in two, and gastrinoma in one). One had metastatic leiomyosarcoma, and the last had an adenocarcinoma of unknown origin. In one of the patients with metastatic carcinoid, a bile duct carcinoma was discovered incidentally in the hepatectomy specimen. The clinical summaries of these cases are shown in Table 5.

The metastatic deposits were multiple in all seven, and in one case the diaphragm was invaded. Of the five patients with neuroendocrine metastases, four underwent synchronous total hepatectomy and resection of the primary lesions (two small bowel resections and two distal pancreatectomies, including the spleen in one case).

Survival

One patient transplanted for metastatic carcinoma died during her third transplant. Her first allograft liver failed after 3 months. Within 3 days of her second transplant, a third was required for primary graft nonfunction. An autopsy showed no demonstrable residual carcinoid tumor. The single patient with the coincidental bile duct cancer died 5 months posttransplant because of the bile duct carcinoma. No recurrence of the carcinoid tumor was evident. A third patient died 21 months after transplantation as the result of recurrent cancer. The other four patients are alive 2 to 28 months after transplant (mean followup 14 months). Each has good allograft function. One of these four surviving patients has developed metastases in the ribs and is receiving chemotherapy.

Pichlmayr's compilation of the data available relative to liver transplantation for malignant tumors from seven European centers included a total of 43 patients with metastatic liver tumors. Thirty of these had colorectal tumors. Twenty-eight per cent of all patients survived one year, and 14 per cent survived for 2 years or more.[10]

In the presence of isolated hepatic metastases, liver transplantation with an intent to cure may be justified in certain special groups of patients: These groups include the following: (1) highly selected patients with disabling symptoms from hepatic metastases of endocrine tumors (glucagonoma, carcinoid, vipoma, gastrinoma, etc.) that grow slowly; (2) patients with selected primary intraabdominal tumors with indolent clinical courses; and (3) children with metastatic tumors responsive to chemotherapy and radiotherapy in whom liver replacement might remove all or most of the disease, permitting control of smaller foci of residual disease elsewhere by other therapeutic modalities (chemotherapy or radiation therapy).

PRESENT STATUS AND FUTURE PROSPECTS

An analysis of the data presented in this article provides evidence that at present, the overall results of total hepatectomy and orthotopic transplantation for extensive hepatic neoplasms are not optimal. In these days

Table 5. *Clinical Summary of Seven Patients Who Underwent Liver Transplantation for Secondary Liver Tumors*

PATIENT	AGE	SEX	TYPE AND LOCATION OF PRIMARY	TIMING AND LOCATION OF RECURRENCE	ADJUVANT TREATMENT	SURVIVAL	CAUSE OF DEATH
OT 473	54	F	Adenocarcinoma of unknown origin	14 mo/skull, spine and pelvis	Chemotherapy radiation therapy	Died/21 mo	Metastatic disease
OT 525	41	M	Glucagonoma of unknown origin	None	Chemotherapy	Alive/29 mo	—
OT 752	52	F	Carcinoid of unknown origin	None	—	Died/3 mo	Died during second retransplantation for rejection and primary nonfunction; no residual tumor
OT 805	35	F	Leiomyosarcoma of small bowel	9 mo/ribs	Chemotherapy radiation therapy	Alive/15 mo	—
OT 926	41	F	Glucagonoma of pancreas	None	—	Alive/10 mo	—
OT 953*	39	M	Carcinoid of small bowel	3 mo/omentum	—	Died/5 mo	Metastatic disease
OT 1156	45	M	Gastrinoma of pancreas	None	—	Alive/2 mo	—

*This patient also had an unsuspected bile duct carcinoma in the hepatectomy specimen

of escalating medical costs and a shortage of donor organs, one has to ask this question: Is it justifiable to pursue efforts in treating such cases with this modality?

The use of cyclosporine and the greater experience with the technical details of the procedure have markedly reduced the number of early postoperative deaths.[21] This has enabled groups to observe these patients for longer intervals, in order to actually assess them for tumor recurrence and to determine the effect of tumor recurrence on long-term survival. This experience has shown us that among the general category of malignant hepatic tumors, there are certain subgroups of patients whose tumors are biologically less virulent, who may be "cured" or have their disease permanently controlled with orthotopic liver transplantation.

Progress has been hampered by a virtual absence of any chemotherapeutic agents that are effective against bile duct carcinoma and hepatocellular carcinoma. New and better chemotherapeutic agents might change this situation.

The immunosuppression transplant patients require depresses their host immunity against neoplastic cells as well as against the allograft resulting in an increased incidence both of de novo malignancies[15] and a decreased ability to destroy preexistent malignant cells.[13] This situation promotes the development of metastases that might otherwise have failed to become established.

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