The Role of Liver Transplantation in Hepatobiliary Malignancy

A Retrospective Analysis of 95 Patients with Particular Regard to Tumor Stage and Recurrence

B. RINGE, M.D., C. WITTEKIND*, M.D., W.O. BECHSTEIN, M.D., H. BUNZENDAHL, M.D., and R. PICHLMAYR, M.D.

From the Medizinische Hochschule Hannover, Klinik für Abdominal und Transplantationschirurgie, and Pathologisches Institut, Hannover, Federal Republic of Germany*

The role of hepatic transplantation in patients with nonresectable liver or bile duct cancer remains a controversial issue. An analysis of 95 consecutive cases was undertaken to evaluate retrospectively the pathological tumor stage—in accordance with the TNM system—and outcome after transplantation. Included were patients with the following diagnoses: hepatocellular carcinoma (n = 52), cholangiocellular carcinoma (n = 10), hepatoblastoma (n = 2), hemangiosarcoma (n = 2), bile duct carcinoma (n = 20), and liver metastases from different primary tumors (n = 9).The overall actuarial survival rate at 5 years was 20.4%. Median survival improved significantly within the last 4 years as compared to the preceding era (18.06 *vs.* 4.0 months). Currently 27 patients are alive, with the longest follow-up more than 12 years. The incidences of residual or recurrent tumor were 27 and 28, respectively. Particularly in patients who underwent transplantation for hepatocellular or bile duct carcinoma without extrahepatic tumor spread, the results were significantly better; median survival time achieved for these two groups were 120 ($p < 0.01$) and 35 months ($p < 0.05$). Prolonged survival without tumor recurrence was not seen in patients with cholangiocellular carcinoma or liver metastases. These results demonstrate clearly that liver transplantation for hepatobiliary malignancy is still justified on the premises of careful patient selection by adequate tumor staging.

MALIGNANT TUMORS of the liver and biliary tract have a poor prognosis with regard to the natural course of the disease. Over the last years, there has been considerable progress in the treatment of these malignancies. [1,2] This is primarily based on recent advances and better understanding of epidemiology, screening for tumor markers, and noninvasive imaging techniques, which lead to more frequent and earlier detection of lesions within the liver parenchyma or hilum, and thereby a higher resectability rate. Furthermore, improvements in patient selection and management, refined techniques in liver surgery, the use of intraoperative sonography, and multidisciplinary approaches have not only contributed to a lower perioperative mortality, but also to improved long-term survival rates.[3]

As compared to any other therapeutic modality, curative tumor removal by resection is without doubt the treatment of choice for patients with primary or secondary hepatic malignancy or biliary tract tumors, currently offering the best chance of survival.[4-8]

However, in cases with nonresectable hepatobiliary malignancy regarding technical reasons (size or location of the tumor, vascular invasion) or impaired hepatic function (*e.g.*, coexisting liver cirrhosis), conventional surgery is limited, and quite often impossible. Overall resectability rates reported in the literature rarely exceed 30–40%.[9,10] For those particular patients, total hepatectomy and subsequent liver replacement can, and has been, considered in the past as offering a true chance for survival and as an almost logical approach, thus extending the criteria of local resectability.[1,11]

One should not forget that in the early trials of human liver transplantation, the very first extended survivals in the world were achieved in tumor patients. At that time, many surgeons regarded primary hepatic malignancy and bile duct carcinoma as unequivocal and even excellent indications for this type of treatment.[12,13] Soon after, it was learned that the vast majority of those patients developed tumor recurrence within the first or second year after transplantation; in most cases only a temporary, but nevertheless quite often significant palliation could be achieved, whereas cure was restricted to very few, and more or less exceptional patients with primary liver tu-

Supported by Deutsche Forschungsgemeinschaft.

Reprint requests and correspondence: Dr. B. Ringe, Medizinische Hochschule Hannover, Klinik für Abdominal und Transplantationschirurgie, Konstanty-Gutschow-Strasse 8, 3000 Hannover 61, Federal Republic of Germany.

Submitted for publication: May 13, 1988.

mors, but was never seen in recipients treated for bile duct cancer.[14-17]

Despite significant improvements in the field of clinical liver transplantation and the much better overall survival rates we see today, the results obtained in this particular group of patients remain disappointing. Especially in light of limited donor resources, there is an ongoing controversial discussion whether tumor patients should be considered as transplant candidates or be absolutely precluded from this approach.[18]

At present, the factors playing a major prognostic role—being either especially advantageous or disadvantageous—are virtually unknown, and it is impossible to predict those patients who are most likely to have prolonged survival without tumor recurrence. Obviously there are only two known exceptions to the generally poor prognosis in cancer patients: incidental hepatomas arising in livers with other diseases, and the fibrolamellar variant of hepatocellular carcinoma.[19]

The following detailed analysis of 95 consecutive patients who received liver transplants for hepatobiliary malignancy since the initiation of our program in 1972 was therefore undertaken to evaluate various factors with possible relevance to the individual as well as to overall prognosis.

In particular, the histologic type of tumor, co-existing liver disease, and tumor stage according to the TNM classification at the time of transplantation were assessed retrospectively and compared to the incidence and pattern of tumor recurrence.

Material and Methods

Within a period of 15 years (November 24, 1972 to December 31, 1987), a total of 341 liver transplantations had been performed in 294 patients. The main indications were benign diseases of various origin (199 patients), whereas malignant tumors accounted for only one third (95 patients). Especially during the last years, there was a clear tendency towards liver replacement in benign end-stage liver disease (Fig 1).

For a detailed retrospective analysis of those 95 patients with malignant hepatobiliary disease, all available data were reviewed with regard to previous medical history, including exploratory laparotomy, treatment before transplantation, and findings at the time of total hepatectomy (intrahepatic tumor size, number and location, vascular invasion or thromboses and extrahepatic spread). To determine the type and stage of the tumor, all specimens taken from the excised livers were re-evaluated microscopically. leading to a pathologic classification in accordance with the TNM system that can be applied to hepatocellular, intra-(cholangiocellular) and extrahepatic bile duct carcinoma.[20] During the postoperative follow-up (minimum 3 months) the pattern of tumor recurrence (time and location) was assessed.

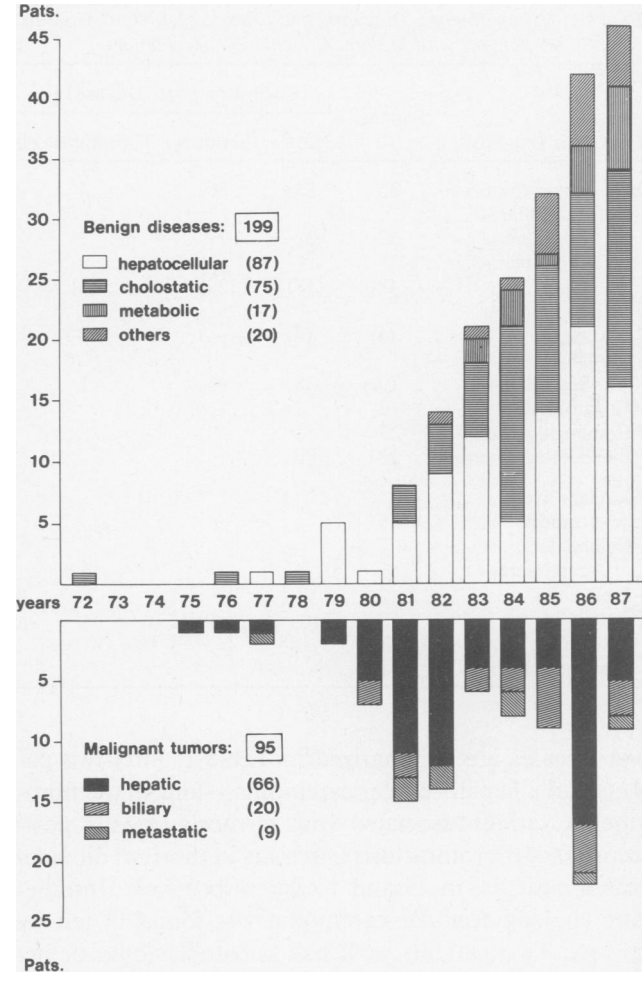

FIG. 1. Indications for liver transplantation in 294 patients with benign diseases and malignant tumors (November 24, 1972–December 31, 1987).

Patient survival was calculated by the life-table method using the Statistical Package for Social Sciences (SPSS, Inc., Chicago, IL). The Lee-Desu statistical analysis was used to compare the cumulative survival function of different groups. P values less than 0.05 were considered statistically significant.

The patients' ages at the time of liver transplantation ranged from 11 months to 71 years (mean of 40.2 ± 13.4 years); there were 25 patients younger than 30 years of age, including three children (under 16 years), whereas the majority of 45 recipients were between 30 and 50 years of age, and 25 patients were older than 50 years. The sex ratio male to female was 60:35.

In 24 cases, basic immunosuppression consisted of azathioprine together with prednisolone and antilymphocyte serum; 71 patients received a combination of cyclosporine A and prednisolone. Eight of 95 patients had one or two retransplantations; indications were initial nonfunction (n = 3), arterial thrombosis (n = 1), acute (n = 2) and chronic rejection (n = 3).

The different histopathologic diagnoses and coexisting

TABLE 1. *Histopathologic Diagnosis and Coexisting Liver Disease in 95 Patients with Malignant Hepatobiliary Tumors*

Histologic Diagnosis	Patients (n)	Coexisting Liver Disease (n)		
		None	Cirrhosis	Thorothrastosis
Primary liver tumors	86	53	30	3
Hepatocellular carcinoma	52	22	29	1
(Nonfibrolamellar type)	(48)	(18)	(29)	(1)
(Fibrolamellar type)	(4)	(4)	(—)	(—)
Cholangiocellular carcinoma	10	8	1	1
Hepatoblastoma	2	2		
Hemangiosarcoma	2	1		
Bile duct carcinoma	20	20		
Secondary liver tumors	9			
Colorectal carcinoma	3			
Melanoma	2			
Carcinoid	2			
GRFoma	1			
Choriocarcinoma	1			

liver diseases are summarized in Table 1. Fifty-two patients had a hepatocellular carcinoma—four of the fibrolamellar variant-associated with cirrhosis (mostly postnecrotic) or thorothrastosis (cirrhosis in thorium dioxide-treated patients) in 29 and 1 case, respectively. Intrahepatic cholangiocellular carcinoma was found in ten recipients. Two patients each had hepatoblastoma or hemangiosarcoma; one of the latter was classified as having epitheloid hemangioendothelioma. Twenty patients received transplants for extrahepatic bile duct carcinoma arising at the bifurcation (the so-called Klatskin tumor). In nine patients with liver metastases, the primary tumors had been carcinoma of the colon and rectum(3), melanoma (2), small intestinal carcinoid (2), jejunal GRFoma (a tumor producing growth hormone releasing factor) (1), and choriocarcinoma of the testicle (1).

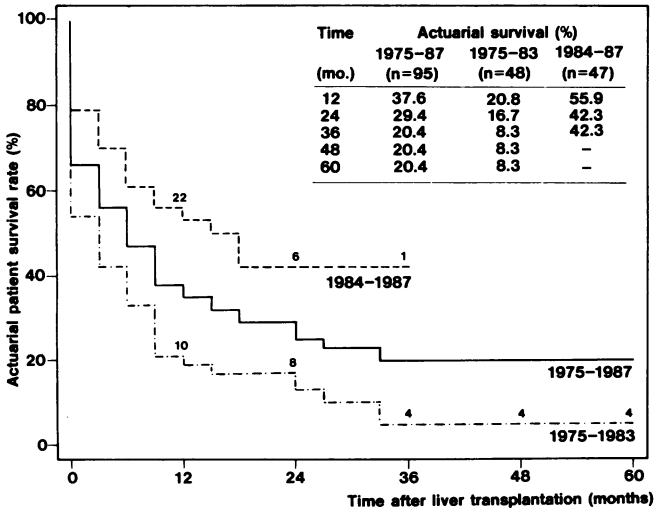

FIG. 2. Overall results of liver transplantation for hepatobiliary malignancy, and comparison of two eras (1975–1983, and 1984–1987).

In the vast majority of patients, the indication for liver replacement was a malignant hepatobiliary disease found preoperatively. There were only few exceptions: one asymptomatic hepatocellular carcinoma found incidentally at transplantation for postnecrotic cirrhosis [liver transplantation (continuous number) (LTx No. 331]; five cases with suspicion of primary sclerosing cholangitis that after histologic examination of the excised liver turned out to be bile duct cancer (LTx Nos. 81, 119, 155, 205, and 302); and one patient with diffuse intrahepatic metastases from a choriocarcinoma that was thought to be a ruptured hemangiomatosis before liver transplantation (LTx No. 47).

Results

Abdominal surgery before liver transplantation had been performed in a total of 66 patients: explorative laparotomy only (to assess local irresectability and extrahepatic tumor spread) (n = 37); portosystemic shunt (n = 2); removal of primary tumor outside the liver (n = 5); various biliary drainage procedures (n = 11); tamponade for bleeding from a ruptured liver tumor (n = 1); hepatic arterial devascularization (n = 1); partial hepatectomy (n = 4); and resection of the proximal bile ducts (n = 5). Twenty-nine patients were not operated on before. Other or additional previous treatment consisted of external or intraluminal irradiation in three cases, and chemotherapy in nine patients, including one case with chemoembolization using lipiodol (iodized oil).

At the time of transplantation, the analysis of various tumor characteristics that were available only after careful pathologic examination of the excised livers and adjacent tissue structures revealed the following information. Tumor size ranged from 0.6 to 23 cm (mean of 8.7 ± 5.1 cm). The lesions were solitary in 19 cases, and multilocular (including solitary nodes with satellites) in 59 livers. In 17 patients—particularly in those with proximal bile duct cancer—the tumor did not invade the liver parenchyma. Intrahepatic location was unilobar (n = 12), bilobar (n = 46), or centrally located (n = 34). Tumor thrombosis or infiltration of the portal vein was found in 19 and five cases, respectively; one patient each had a tumor infiltration of the hepatic artery or inferior vena cava. There were 27 patients with extrahepatic spread to regional lymph nodes (n = 24) and/or distant metastases (n = 8) who were defined as having residual tumor after total hepatectomy.

Actuarial survival rates of all 95 patients at 1, 2, and 5 years after liver replacement were 37.6, 29.4, and 20.4%, respectively (Fig. 2). Neither age nor sex of the recipient nor kind of immunosuppression alone had any significant influence on short- or long-term outcome. However,

looking at two consecutive eras, there was a highly significant difference in patient survival; 30-day mortality during 1975–1983 was 29.2% (median survival of 4 months) as compared to 17% during 1984–1987 (median survival of 18.06 months). Even when those 22 patients who died within 30 days after transplantation were excluded from the analysis (to get a better impression of the long-term prognosis) the two eras could clearly be distinguished, with a median survival of 8.67 *versus* 37 months ($p < 0.01$). These results reflect not only improvement in perioperative management, but also patient selection regarding the tumor stage over the years.

Comparison of survival rates according to the histologic type of tumor did not show significant differences, especially considering that the number of long-term survivors was rather small (Fig. 3). The corresponding median survival times are listed in Table 2. Apart from the aforementioned 27 cases with extrahepatic tumor spread found at the time of transplantation, the overall incidence of tumor recurrence was 28 of 95 patients. Organs involved mainly by distant metastases were liver (n = 26), lung (n = 17), peritoneum (n = 16), and bone (n = 10).

In several patients, treatment of recurrent neoplasm involved chemotherapy, irradiation, and surgery; definite cure was achieved in only one case after pulmonary lobectomy (LTx No. 2).

The major causes of death in 68 liver recipients were tumor recurrence (n = 29), sepsis (n = 15), and rejection (n = 8). At present, 27 patients are alive with a postoperative follow-up of 3 months to more than 12 years.

The characteristic data in relation to the different tumor types will now be described separately in more detail.

Hepatocellular Carcinoma

In the majority of 52 patients who underwent transplantation for hepatocellular carcinoma, the intrahepatic tumor was advanced, most being larger than 5 cm in diameter (n = 37), multilocular (n = 41), and with bilobar or central location (n = 43); 39 cases were thus clarified as pathologic tumor classification (TNM classification)[20] (pT) 4 (Table 3). One patient (LTx No. 245) had had a previous extended lobectomy with suspected residual tumor so that complete removal of the remaining liver and transplantation was carried out. Thorough pathologic examination, however, did not show any tumor left which explains pT 0. Histopathologic grading revealed the following differentiation of tumors: well-differentiated (G 1) in 10, moderately differentiated (G 2) in 31, and poorly differentiated (G 3) in 2 cases, respectively. Tumor thrombosis of the portal vein—seen in 17 patients—was more frequent in hepatocellular carcinoma coexisting with cirrhosis (14 of 29 patients, 48.3 %). Extrahepatic tumor growth to regional lymph nodes (pN 1) was found in eight cases; the occurrence of distant metastases (pM 1) could be assessed only during operation or autopsy (n = 5), and was therefore unknown in most cases [presence of distant metastasis cannot be assessed (pMX)].

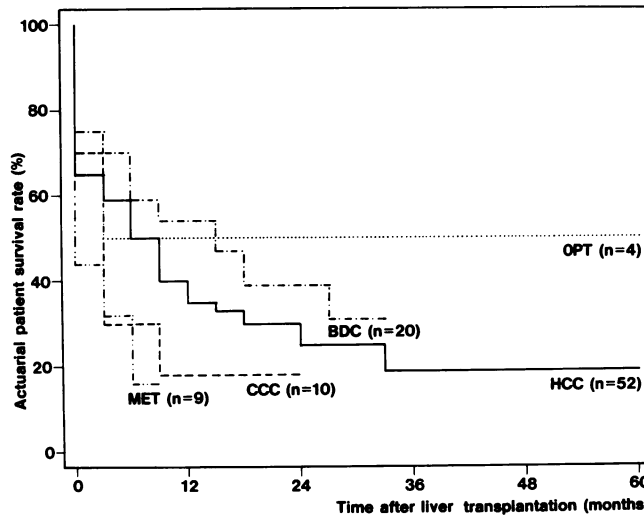

FIG. 3. Results of liver transplantation according to the histologic type of tumor. (HCC = hepatocellular carcinoma, CCC = cholangiocellular carcinoma, OPT = other primary liver tumors, BDC = bile duct carcinoma, MET = liver metastases).

Classification according to TNM led to stage grouping with highly significant differences in median survival time: 120 months for stage II (pT2 pNO pMO) as compared to 11.88 months for stage III (pT1-3pNO-1 pMO) and 8.75 months for stage IVA (pT4 pNO-1pMO) (Fig. 4). All patients grouped as stage IVB (pT1-4pNO-1pM1) died within 2 months (median survival of 0.63 months). Breakdown of the pN category only resulted in a 2-year survival rate of 36.1% (30-day mortality excluded: 46.8%) for pNO cases; by contrast, no patient with lymph node

TABLE 2. *Results of Liver Transplantation for Hepatobiliary Malignancy and Survival and Incidence of Residual/Recurrent Tumor*

Type of Tumor	Patients (n)	Median Survival (mos.)	Incidence of Residual/Recurrent Tumor (n)	Patients Alive (n)
Hepatocellular carcinoma (HCC)	52	8.94	11/16	15
Cholangiocellular carcinoma (CCC)	10	4.00	4/5	1
Other primary tumors (OPT)	4	74.00	−/1	2
Bile duct carcinoma (BDC)	20	16.57	7/3	8
Metastases (MET)	9	1.50	5/3	1
Total	95	8.25	27/28	27

TABLE 3. *pTNM Classification and Median Survival of 52 Patients with Hepatocellular Carcinoma*

pT	Patients (n)	Median Survival (mos.)	pN	Patients (n)	Median Survival (mos.)	pM	Patients (n)	Median Survival (mos.)	Stage	Patients (n)	Median Survival (mos.)
0	1		0	35	9.5	0	10	2.00	0	1	
2	4	120.00							II	4	120.00
		$p < 0.05$			$p < 0.05$			$p < 0.05$			$p < 0.01$
3	8	11.00	1	8	2.00				III	6	11.88
		$p < 0.05$									
4	39	8.37				1	5	0.63	IVA	36	8.75
									IVB	5	0.63

(pNX = 9; pMX = 37)

metastases (pN1) survived beyond 1 year ($p < 0.05$; Fig 5). Although the results were obviously more favorable in stage II, it has to be mentioned that two of those four patients experienced tumor recurrence; one could be cured by pulmonary lobectomy (LTx No. 2) and has survived for more than 12 years, whereas the other is still at risk with progressive metastases to lymph nodes and liver despite chemotherapy and several attempts of complete surgical tumor removal (LTx No. 102).

In this analysis, preoperative serum alpha-fetoprotein (AFP) levels (mean of 253.2 ± 254.0 ng/ml), which were normal in 14 recipients and elevated in 35 others, did not have a significant correlation with postoperative outcome (median survival of 18.63 *vs.* 8.74 months). However, determination of this tumor marker seemed to be at least of some prognostic value; looking at a subgroup of ten patients with preoperatively high AFP levels, in the majority of cases, AFP dropped soon after transplantation but reappeared or rose early—generally within 3–4 months, and correlated with tumor recurrence in all patients (Fig. 6). Moreover, tumor-free long-term survivors were particularly those with normal or only slightly elevated AFP levels before liver replacement.

In general, coexistence of cirrhosis was not associated with a better or worse survival rate, except in that the 30—day mortality was higher than in noncirrhotic patients (34.5% *vs.* 13%).

Two of four patients with fibrolamellar hepatocellular carcinoma had residual tumor (positive lymph nodes); one further recipient had early recurrence, and only one recipient has been alive without tumor for 30 months.

The relation of preoperative status (TNM, AFP) to postoperative outcome (pattern of tumor recurrence, treatment, and cause of death) is shown in detail in Figures 7 and 8 for those 39 patients with hepatocellular carcinoma surviving for more than 30 days. There were two patients (LTx Nos. 115 and 116) with large multilocular hepatocellular carcinoma in cirrhosis who received adjuvant systemic chemotherapy (FUDR) via an implanted Infusaid pump (Infusaid Corp., Norwood), starting 5 weeks post-transplantation. In both cases, tumor recurrence could not be prevented.

Cholangiocellular Carcinoma

Four of ten patients with cholangiocellular carcinoma had extrahepatic tumor at the time of liver transplantation. A tumor thrombus of the portal vein was present in two patients, one of whom had coexisting cirrhosis. In all

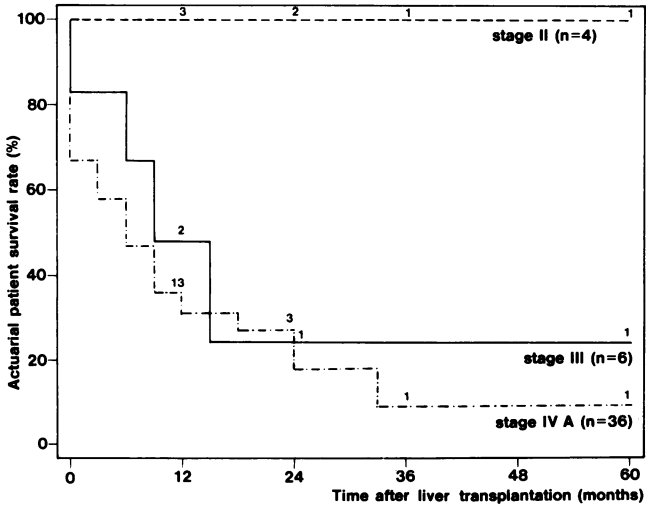

FIG. 4. Results of liver transplantation for hepatocellular carcinoma according to TNM stage (patients with stage O or IVB are excluded).

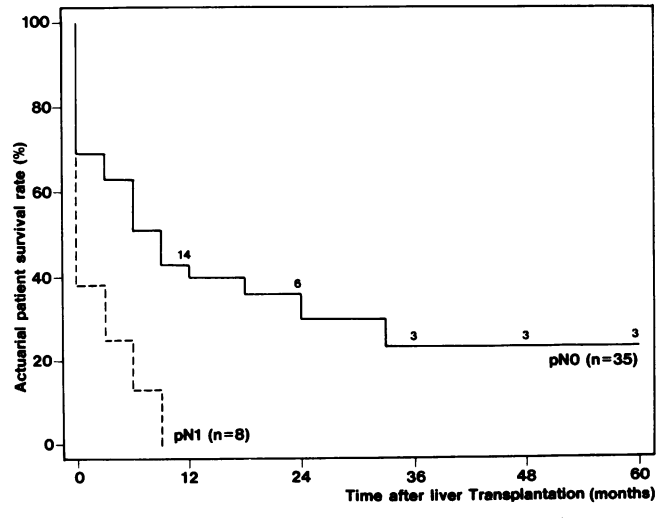

FIG. 5. Results of liver transplantation for hepatocellular carcinoma according to pN classification.

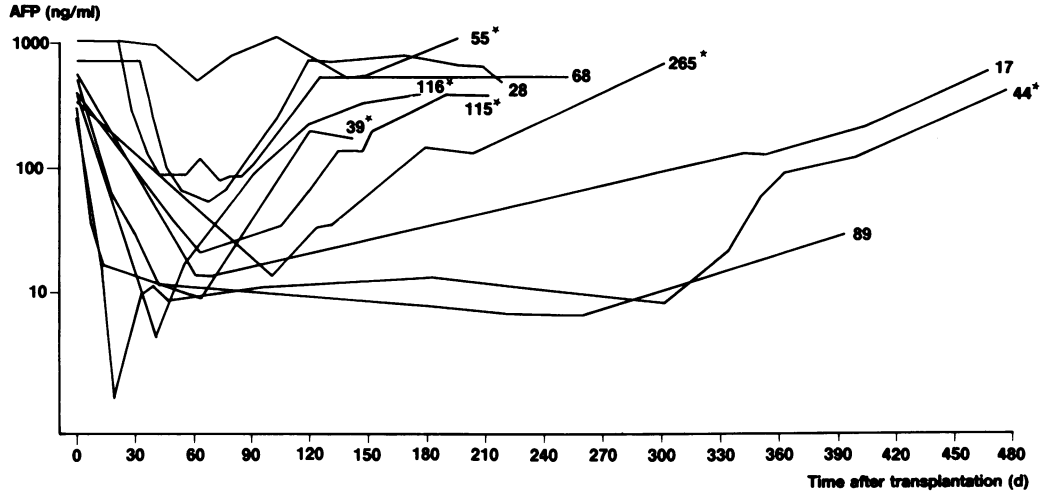

FIG. 6. Serum alpha-fetoprotein (AFP) levels before and after liver transplantation in ten patients (LTx No.) with hepatocellular carcinoma (and coexisted cirrhosis *), and tumor recurrence (AFP: normal range < 16 ng/ml).

recipients surviving for more than 30 days, widespread distant metastases developed in liver, lung, and particularly in bone (Fig. 9).

With one exception only—a patient with stage II tumor who lived for 25 months (LTx No. 75)—the remaining recipients have died in less than 1 year, the majority even within the first 6 months after transplantation, because of early tumor recurrence. At present only one patient is alive, but with multiple pulmonary metastases. A meaningful statistical analysis for this small group of patients could not be performed.

Other Primary Liver Tumors

One of the two patients with hepatoblastoma was an 11-month-old child with multiple mixed epithelio-mesenchymal type lesions in both liver lobes who is currently alive and free of tumor more than 6 years after transplantation. The other recipient died of septicemia during the early postoperative period.

There were two cases each of hemangiosarcoma—one associated with thorothrastosis, the other having a solitary centrally located tumor classified as epitheloid hemangioendothelioma. The first patient died 5 months later due to disseminated tumor metastases in liver, lungs, pleura, peritoneum, and bone. The latter patient is alive and well without recurrence after 3 years.

Bile Duct Carcinoma

Pathologic classification of bile duct carcinoma according to TNM demonstrated nine cases with T2 and eleven with T3. Extrahepatic tumor was present in seven recipients, two of whom had not only regional lymph node

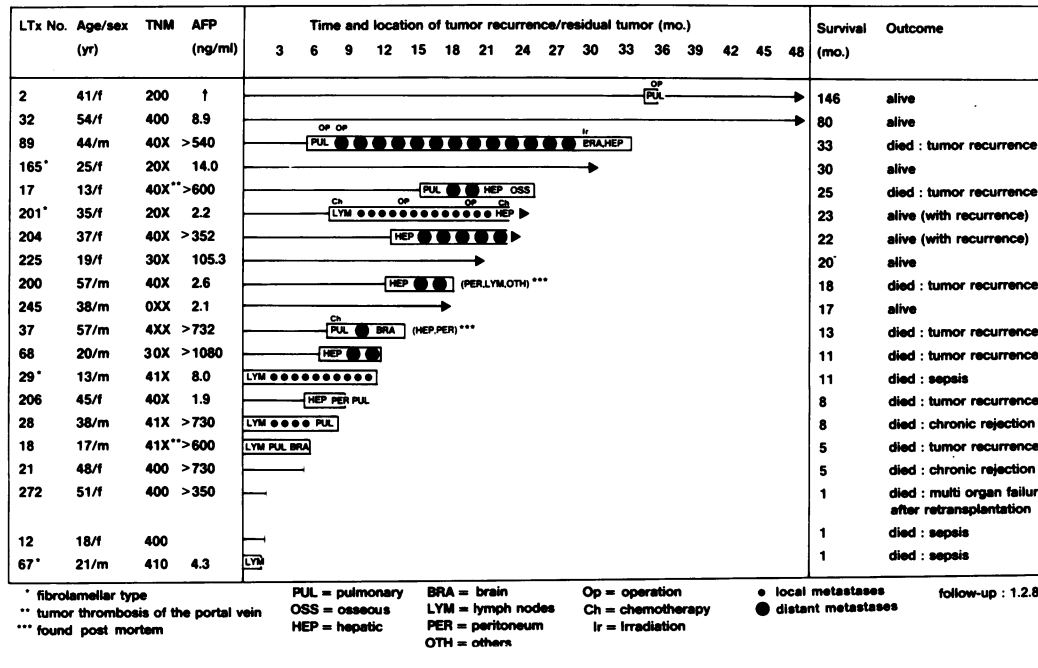

FIG. 7. Liver transplantation in 20 patients with hepatocellular carcinoma (three patients who died within 30 days are excluded).

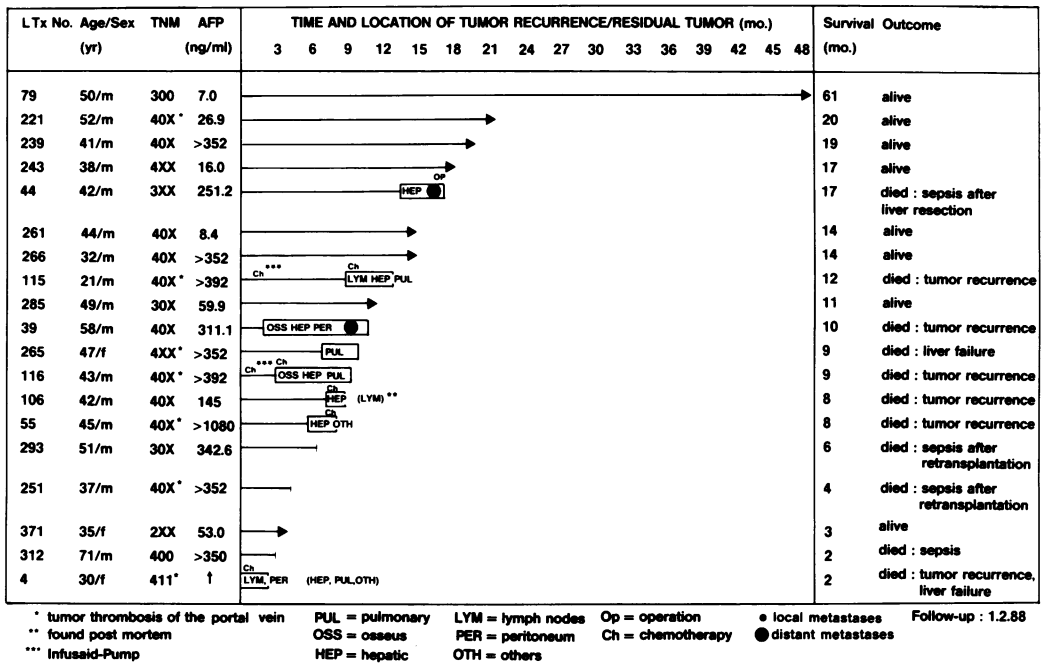

FIG. 8. Liver transplantation in 19 patients with hepatocellular carcinoma and cirrhosis (ten patients who died within 30 days are excluded).

but also distant metastases. The following stages could be appointed to these categories: II (pT2 pNO pMO; n = 8) III (pT1–2 pN1 pMO; n = 1), IV A(pT3 pNO–1 pMO; n = 9), and IV B (pT1–3 pNO–1 pM1; n = 2).

The major and significant influence on survival was shown to be the lymph node status free of tumor (pNO as compared to infiltrated, pN1 with median survival times of 35 *vs.* 7.25 months). The 2-year actuarial survival rate in the former group of recipients was 64.1% (Fig. 10). At present, eight patients are alive, seven without any sign of tumor recurrence (maximum follow-up of 35 months).

By contrast, all recipients with regional lymph node metastases found at the time of transplantation had a limited survival span, generally far less than 1 year. The patient who survived longest in this group died after 16 months. Diffuse carcinomatosis of the peritoneal cavity was not at all rarely found at reoperation or autopsy (Fig. 11).

Secondary Liver Tumors

Hepatic metastases of primary tumors outside the liver that were considered an indication for transplantation, particularly in earlier years, had various origins (Table 4). In two cases, the definite diagnosis of secondary liver tumor was not known before transplantation; instead, hepatocellular carcinoma (LTx No. 123) and ruptured hemangiomatosis (LTx No. 47) were suspected previously. Four of those nine patients died within 30 days, due to reasons not related to the malignant disease. Four additional recipients had residual or recurrent tumor; so far, the longest survival that has been observed is 10 months.

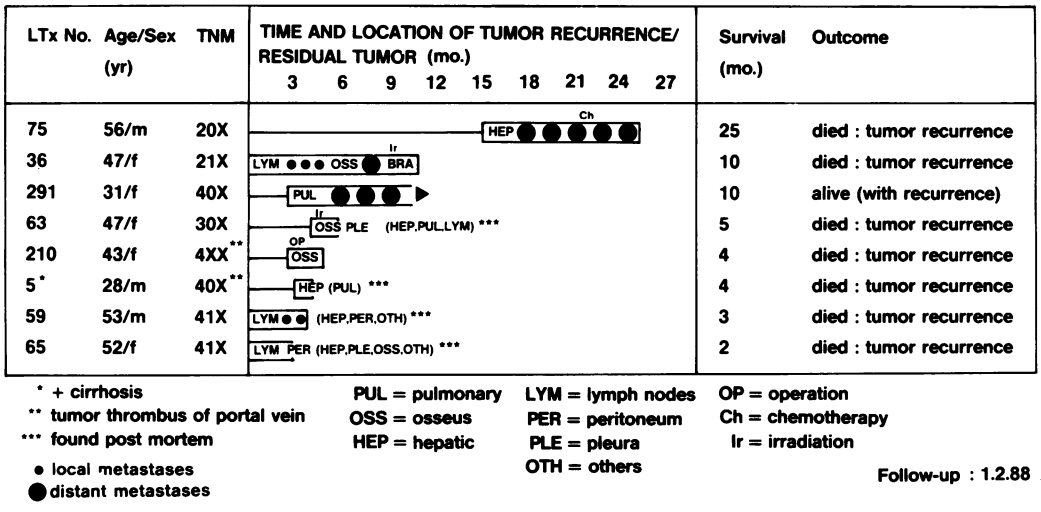

FIG. 9. Liver transplantation in eight patients with cholangiocellular carcinoma (two patients who died within 30 days are excluded).

Currently there is only one survivor (LTx No. 325). The primary tumor of this 18-year-old female, which was located in the jejunum and had been removed more than 3 years before liver transplantation, was classified as neuroendocrine malignoma producing growth hormone-releasing factor (so-called GRFoma). Multiple synchronous liver metastases could be controlled temporarily by continuous application of a somatostatin-analogous drug. However, because total hepatectomy was being considered as the only curative treatment of the disease, liver transplantation was carried out. Currently, the patient is well and has had no recurrence, but normal levels of growth hormone and growth releasing factor.

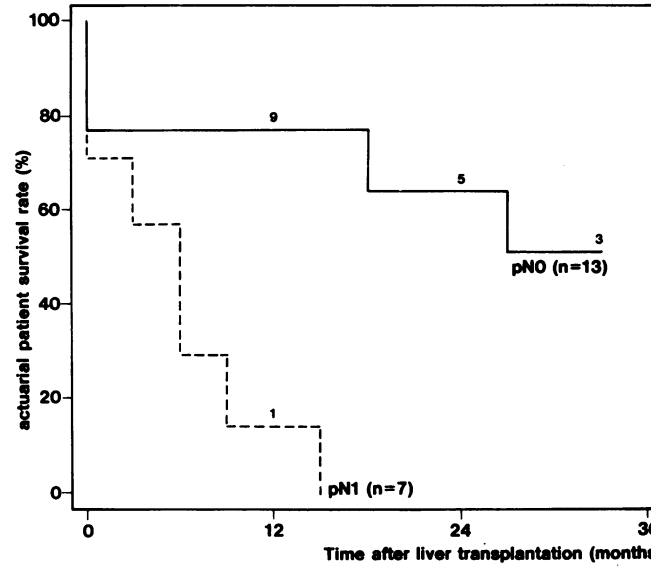

FIG. 10. Results of liver transplantation for proximal bile duct carcinoma according to pN classification.

Discussion

Regarding the therapeutic strategy for hepatobiliary malignancy, it is widely accepted now that surgery—partial hepatectomy or/and bile duct resection—is the treatment of choice. At present, this approach offers by far the most favorable long-term results, especially when the tumor removal can be considered as curative. For primary or secondary liver tumors, actuarial 5-year survival rates in the range of 20–50% are reported from various authors.[4,5,7,21] In patients with proximal bile duct cancer, similar results may be achieved.[8,22]

The value of preoperative and adjuvant chemotherapy or treatment protocols combining resection with other techniques (*e.g.*, transcatheter arterial embolization, radiation, and immunotherapy) is not yet clearly visible but seems to be of advantage under certain circumstances, such as coexisting liver cirrhosis, or in special studies.[23,24]

Even nowadays, with advanced techniques and expertise, most surgeons are confronted with resectability rates that rarely exceed 30–40%. The crucial question is: what to do with liver or bile duct tumors that are clearly nonresectable from the technical point of view or because of impaired hepatic function? It remains a controversial issue whether these particular patients should be considered for total hepatectomy and liver transplantation.[11,18,25]

The pro's are: unavailability of effective alternative therapy, considerable palliation in many, and obvious cure in at least some patients. Yet the con's also have to be mentioned: tumor recurrence in the majority of cases, inadequate knowledge of the biological and anatomic factors relevant for a good long-term prognosis, and last but

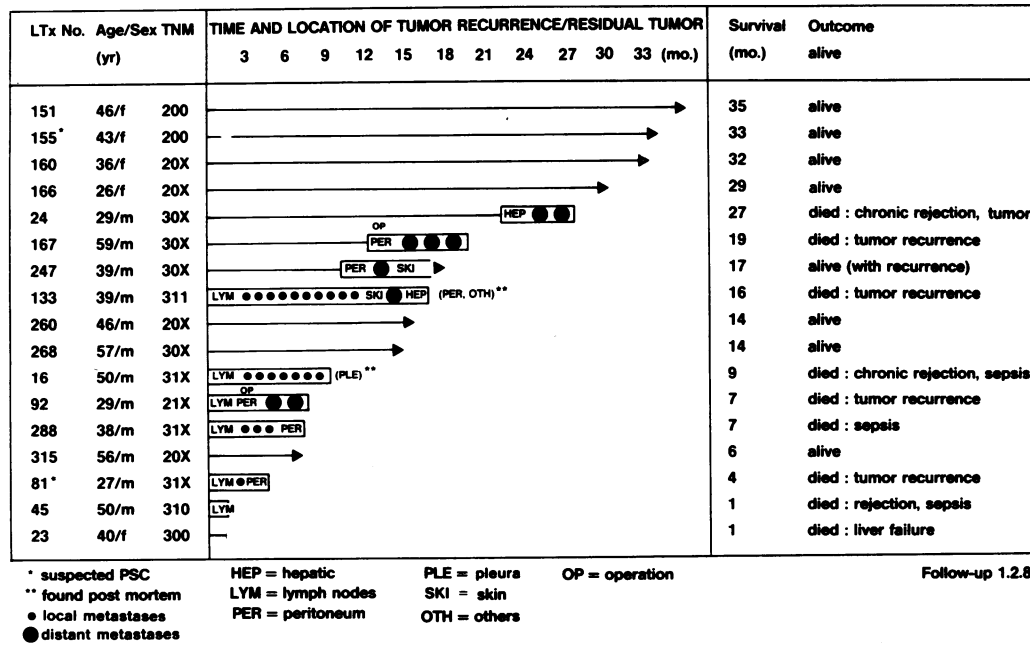

FIG. 11. Liver transplantation in 17 patients with proximal bile duct carcinoma (three patients who died within 30 days are excluded).

TABLE 4. *Liver Transplantation in Nine Patients with Hepatic Metastases*

LTX No.	Age (years)/Sex	Primary Tumor	Survival	Outcome
7	42/F	Rectum carcinoma	10 mos.	Died of tumor recurrence (liver, lungs)
254	59/F	Carcinoid (ileum)	6 mos.	Died of tumor recurrence, sepsis
135	24/F	Melanoma (eye)	4 mos.	Died of tumor recurrence (skin, bone, liver)
325	18/F	GRFoma (jejunum)	4 mos.	Alive (no recurrence)
47	21/M	Choriocarcinoma (testicle)	1 mos.	Died of residual tumor (lymph nodes, retroperitoneum, liver, lung)
77	51/F	Carcinoid (ileum)	10 days	Died of cardiac failure
41	25/M	Rectum + sigmoid carcinoma	9 days	Died of hepatic artery thrombosis
123	61/M	Melanoma	9 days	Died of sepsis
50	44/M	Colon carcinoma	8 days	Died of acute rejection

not least, the limited donor resources that might restrict this treatment to those patients who are most likely to benefit from the approach.

Because liver transplantation has come of age and become a service in many centers, now it seems not only worthwhile but necessary to elucidate at least some of the problems that have not yet been clarified sufficiently. Among many others, this holds true also for the question of total hepatectomy and liver replacement in cancer patients. As in most North American and European centers also in our hands, liver transplantation is being regarded as the treatment of choice, particularly for benign end-stage liver diseases.[26-28]

Since the liver transplant program in Hannover was initiated in 1972, a reasonable number of candidates have received liver grafts for malignant diseases. Within the same period, even more patients with hepatobiliary malignancies have been treated conventionally by partial hepatectomy and/or bile duct resection at this institution. Thus, our personal view has not been directed exclusively towards transplantation under all circumstances; rather, whenever possible, liver resection has been chosen as the first option, whereas total hepatectomy and liver replacement have been taken into consideration as alternative procedures in nonresectable cases only.[21,22]

It was the aim of the present retrospective analysis of 95 consecutive liver recipients to look for particularly favorable or unfavorable prognostic factors—with special emphasis on tumor classification and staging according to the TNM system, which has not been done before, and to make this experience available to other groups.

Our own overall results after liver transplantation for cancer, regardless of era, immunosuppression, histopathologic diagnosis, or tumor stage are well in accordance with those of other centers; long-term survival rates of approximately 20–30%—which after a 5-year follow-up can perhaps be regarded as cure—have been reported from Pittsburgh as well as from Cambridge, with the incidence of tumor recurrence being in the range of 50–80%.[16,27,29,30]

Comparing those data obtained from cases of hepatobiliary malignancy with the generally known and accepted survival rates of other gastrointestinal (G.I.) tumors (*e.g.*, esophageal, gastric, or pancreatic carcinoma), one has to take into consideration that with radical surgery also being practiced for the latter tumors, the results after liver transplantation in general can by no means be called disastrous and unacceptable.

Stratification into different periods shows a significant improvement more recently, with the 3-year actuarial survival rate since 1984 reaching 42.3 %. This progress is primarily based on lower perioperative mortality and better patient selection, but may also be influenced by more effective immunosuppression, as has been shown by Iwatsuki[16] when comparing the so-called precyclosporine and cyclosporine eras.

It was clearly demonstrated by the same group that hepatic tumors coincidental with other liver diseases had a much better prognosis, with only one tumor recurrence being seen to date.[27] Comparable data from our own patient population are not available because the incidence of malignancy unknown before liver transplantation was very low; only one patient had an asymtomatic hepatocellular carcinoma found incidently after liver replacement for postnecrotic cirrhosis, and her follow-up is too short for any conclusions to be drawn. However, there were five cases with suspected primary sclerosing cholangitis that were later shown to be proximal bile duct cancer. This finding is not totally surprising because the histologic diagnosis of this particular tumor is often confirmed only after surgical removal.

The value of performing an exploratory laparotomy before liver transplantation to rule out extrahepatic tumor spread has not yet been proven without doubt. Krom et al.[31] strongly advocated this approach, leading to a very stringent selection of tumor patients, and also Calne[29] recommended that a "mini-laparotomy" be performed routinely before making a decision to proceed with transplantation. However, a recent analysis from the same center questions this approach, particularly because staging laparotomy has failed to predict those patients who will benefit from total hepatectomy.[30] In the past, we have made a similar observation concerning safe assessment of tumor stage and the implications for tumor recurrence after transplantation. There are two major reasons for this dilemma: first, the interval between staging laparot-

omy and liver transplantation is hardly foreseen, and may be prolonged to several months so that tumor progression may be possible in the meantime; and second, extrahepatic "micrometastases" may already be present, but cannot be assessed properly. Nevertheless, several patients referred for exploratory laparotomy do certainly benefit from this approach, even more so because resectable tumors are sometimes found and conventional surgery can be applied.[31]

The possibility that the growth of residual tumor could be accelerated as a consequence of immunosuppression, which was mentioned by Starzl,[11] cannot be denied completely, although our present data and those of others do not clearly support this hypothesis; tumor progression after transplantation is indeed almost comparable to the natural course of the disease, with recurrence being seen mostly within the first postoperative year.[2,4] However, to estimate the influence of immunosuppression, much more experience will be needed in future.

The results after liver transplantation for hepatocellular carcinoma are comparable in principal with data reported from the literature regarding not only a rather high early postoperative mortality (within 30 days) for patients with coexisting cirrhosis—seen particularly during earlier years—but also the long-term survival rate.[27,30] At present, eleven of our 52 patients are alive without recurrence more than 1 year after transplantation, with the patient who has survived the longest having a follow-up of over 12 years.

The fibrolamellar variant seems to be associated with a more favorable prognosis as concerns survival and incidence of tumor recurrence.[32] In our small series, there were only two patients without residual tumor, one of whom is alive and has been tumor-free for 30 months.

What has not been shown before is the statistically significant correlation between pathologic classification and staging according to the TNM system and actuarial survival rate. Patients with T2 N O M O, stage II or III, respectively, had a clearly better prognosis as compared with those who had tumors classified as T4 or with extrahepatic growth (N 1 and/or M 1). This can clearly be taken as strong argument in favor of an accurate preoperative assessment of tumor stage.

As has been demonstrated, serum AFP measured preoperatively, and particularly normalization postoperatively, is a leading prognostic factor after resection for hepatocellular carcinoma.[3,33] This seems to be relevant also in liver-transplanted patients, where failure to decline or early reappearance of AFP is associated with tumor recurrence.[34]

Our own experience with cholangiocellular carcinoma was extremely disappointing; either residual tumor or early and mostly widespread recurrence precluded tumor-free survival. However, long-term survivors have been reported by various groups.[18]

The natural course of other primary liver tumors (*e.g.*, hepatoblastoma in children or epitheloid hemangioendothelioma), is quite often unpredictable. Therefore, the question of whether to proceed with liver transplantation in those patients cannot be answered in general, but has to be decided individually, particularly since prolonged survival can be achieved.[35]

Within recent years, the therapeutic approach for proximal bile duct carcinoma has changed in many groups now being mainly directed at radical surgery. Whenever this cannot be accomplished by resection of the hilum alone or combined with partial hepatectomy. liver transplantation may be indicated.[22,36] Our experience with this strategy, which has been published previously, now includes 20 patients.

The actuarial survival rates obtained were significantly better in recipients without tumor-infiltrated regional lymph nodes; currently there are seven patients alive and tumor-free, four of whom were tumor-free 29–35 months after transplantation. It is noteworthy that in a most recent analysis from the Pittsburgh group, Iwatsuki reported that no patient with bile duct cancer has lived 2 years postoperatively.[27] Although our follow-up period is still rather short and the number of our patients is small, our study clearly demonstrates that prolonged survival can be achieved. Without question it is too early to say whether cure of those patients will be possible, since up until now it has never been seen before.

The results of liver transplantation for metastases have indeed been disastrous in most centers. So far, none of our patients survived beyond 10 months, and currently only one is alive. However, exceptional prolonged survival has been documented over the years.[37]

Our present opinion is that secondary liver tumors should be regarded as indication for transplantation only when combined treatment protocols, such as those tried by the Innsbruck group, are available. The question is whether metastatic lesions from specific (*e.g.*, neuro-endocrine) tumors might be more suitable.[27,38]

In conclusion, despite great disappointment, particularly in the past, hepatobiliary malignancy should not be regarded as contraindication for liver transplantation *per se*. On the contrary, this approach is certainly justified and should play a role in the overall therapeutic strategy, thus extending the limitations of conventional surgery. However, extremely careful patient selection is essential, as is taking into consideration all factors that might be relevant to the prognosis. At present, this includes thorough screening and accurate tumor staging before transplantation to identify those patients who are most likely to have long-term survival without tumor recurrence.

As regards other malignancies, in the future, multimodality treatment protocols combining total hepatectomy with preoperative or adjuvant chemoimmunotherapy or other techniques will be needed. At least there is

hope that chemo- or immunotherapy will contribute to an improvement of the present situation after liver transplantation for hepatobiliary malignancy and that this will result not only in palliation, but cure of more patients than we see nowadays.

Addendum

Since this manuscript was originally submitted, the follow-up period for patients alive at February 1, 1988 has extended to November 1, 1988. Within these 9 months, seven recipients have died of tumor recurrence, leaving a total of 20 of 95 patients presently alive. To allow identification of those cases, the successive liver transplant numbers are given, and can be compared with the corresponding Figures 7, 8, 9, and 11: LTx Nos. 201, 204, 79, 285, 291, 166, and 268.

Two patients of particular interest are those who developed late tumor recurrence after hepatectomy for hepatocellular carcinoma and coexisting cirrhosis (LTx No. 79, more than 5 years), and for proximal bile duct cancer (LTx No. 166, more than 3 years). These latest results emphasize again the uncertainty as to what extent long-term cure can be expected after liver transplantation for hepatobiliary malignancy.

References

1. Foster JH, Berman MM. Solid Liver Tumors. Philadelphia, London, Toronto: WB Saunders Co., 1977.
2. Okuda K, Ishak KG. Neoplasms of the Liver. Tokyo, Berlin, Heidelberg, New York, London, Paris: Springer Verlag, 1987.
3. Tang Z. Subclinical Hepatocellular Carcinoma. Berlin, Heidelberg, New York, Tokyo: Springer Verlag, 1985.
4. Fortner JG, MacLean GJ, Kim DK, et al. The seventies' evolution in liver surgery for cancer. Cancer 1981; 47:2162–2166.
5. Iwatsuki S, Shaw BW Jr, Starzl TE. Experience with 150 liver resections. Ann Surg 1983; 197:247–253.
6. Pichlmayr R, Neuhaus P, Brlsch C. Die Chancen einer chirurgischen Behandlung von Lebertumoren. Verh Dtsch Krebs Ges 1984; 5: 473–482.
7. Adson MA, van Heerden JA. Major hepatic resection for metastatic colorectal cancer. Ann Surg 1980; 191:576–583.
8. Beazley RM, Hadjis N, Benjamin IS, Blumgart LH. Clinical pathological aspects of high bile duct cancer. Ann Surg 1984; 199:623–636.
9. Bismuth H, Houssin D, Ornowski J, Meriggi F. Liver resections in cirrhotic patients: a western experience. World J Surg 1986; 10: 311–317.
10. Okamoto E, Tanaka N, Yamanaka N, Toyosaka A. Results of surgical treatments of primary hepatocellular carcinoma: some aspects to improve long-term survival. World J Surg 1984; 8:360–366.
11. Starzl TE, Koep LJ. Surgical approaches for primary and metastatic liver neoplasms, including total hepatectomy with orthotopic liver transplantation. Prog Clin Cancer 1978; 7:181–193.
12. Starzl TE, Groth CG, Brettschneider C, et al. Extended survival in 3 cases of orthotopic homotransplantation of the human liver. Surgery 1986; 63:549–556.
13. Calne RY, Williams R. Liver transplantation in man. I. Observations on technique and organization in 5 cases. Brit Med J 1968; 4: 535–540.
14. Calne RY. Liver transplantation for liver cancer. World J Surg 1986: 76–80.
15. Iwatsuki S, Klintmalm GBG, Starzl TE. Total hepatectomy and liver replacement (orthotopic liver transplantation) for primary hepatic malignancy. World J Surg 1982; 6:81–85.
16. Iwatsuki S, Gordon RD, Shaw BW Jr, Starzl TE. Role of liver transplantation in cancer therapy. Ann Surg 1985; 202:401–407.
17. Neuhaus P, Broelsch C, Ringe B, Pichlmayr R. Liver transplantation for liver tumors. *In* C Herfarth, P Schlag, P Hohenberger, eds. Recent Results in Cancer Research 100, Therapeutic Strategy in Primary and Metastatic Liver Cancer. Berlin, Heidelberg, New York; Springer Verlag, 1986; 221–228.
18. Pichlmayr R. Is there any place for liver grafting in malignancy? Transplant Proc 1988; 20 (suppl) 1:478–482.
19. Starzl TE, Iwatsuki S, Van Thiel DH, et al. Evolution of liver transplantation. Hepatology 1982; 2:614–636.
20. Hermanek P, Sobin LH. TNM Classification of Malignant Tumors. Berlin, Heidelberg, New York, London, Paris, Tokyo: Springer Verlag, 1987.
21. Pichlmayr R, Ringe B, Bechstein WO, et al. Approach to primary liver cancer. *In* P Schlag, P Hohenberger, U Netzger, eds. Recent Results in Cancer Research 110, Combined Modality Therapy of Gastrointestinal Tract Cancer. Berlin Heidelberg, New York, London, Paris, Tokyo: Springer Verlag, 1988; 65–73.
22. Pichlmayr R, Ringe B, Lauchart W, et al. Radical resection and liver grafting as the two main components of surgical strategy in the treatment of proximal bile duct cancer. World J Surg 1988; 12:68–77.
23. Shimamura J, Gunven P, Takenaka Y, et al. Combined peripheral and central chemoembolization of liver tumors. Cancer 1988; 61:238–242.
24. Sitzmann JV, Order SE, Klein JC, et al. Conversion by new treatment modalities of nonresectable to resectable hepatocellular cancer. J Clin Oncol 1987; 5:1566–1573.
25. Søreide O, Czerniak A, Blumgart CM. Large hepatocellular cancer: hepatic resection or liver transplantation? Brit Med J 1985; 291: 853–857.
26. Bismuth H, Castaing D, Ericzon BG, et al. Hepatic transplantation in Europe. Lancet 1987; 2:674–676.
27. Iwatsuki S, Starzl TE, Todo S, et al. Experience in 1000 liver transplants under cyclosporine/steroid therapy: survival report. Transplant Proc 1988; 20 (suppl 1):498–504.
28. Pichlmayr R, Ringe B, Lauchart W, Wonigeit K. Liver transplantation. Transplant Proc 1987; 19:103–112.
29. Calne RY, Williams R, Rolles K. Liver transplantation in the adult. World J Surg 1986; 10:422–431.
30. O'Grady JG, Polson RJ, Rolles K, et al. Liver transplantation for malignant disease. Ann Surg 1988; 207:373–379.
31. Krom RAF, Gips CH, Houthoff HJ, et al. Orthotopic liver transplantation in Groningen, The Netherlands (1979–1983). Hepatology 1984; 4:61S–65S.
32. Starzl TE, Iwatsuki S, Shaw BW Jr, et al. Treatment of fibrolamellar hepatoma with partial or total hepatectomy and transplantation of the liver. Surg Gynecol Obstet 1986; 62:145–148.
33. McIntire KR, Vogel CL, Primack A, et al. Effect of surgical and chemotherapeutic treatment on alphafetoprotein levels in patients with hepatocellular carcinoma. Cancer 1976; 37:677–683.
34. Ericzon BG, Gustafsson SA, Ludgren G, et al. Early doxorubicin treatment of tumor recurrence after liver transplantation for hepatocellular carcinoma: a case report. Clin Transplant 1987; 1: 265–268.
35. Ishak KG, Sesterhenn IA, Goodman MZD, et al. Epitheloid hemangioendothelioma of the liver: a clinicopathologic and follow-up study of 32 cases. Hum Pathol 1984; 15:839–885.
36. Bismuth H, Castaing D, Traynor O. Resection or palliation: priority of surgery in the treatment of hilar cancer. World J Surg 1988; 12:39–47.
37. Mhlbacher F, Piza F. Orthotopic liver transplantation for secondary malignancies of the liver. Transplant Proc 1987; 19:2396–2398.
38. Margreiter R, Niederwieser D, Frommhold H, et al. Tumor recurrence after liver transplantation followed by high-dose cyclophosphomide, total body irradiation, and autologous bone marrow transplantation for treatment of metastatic liver disease. Transplant Proc 1987; 19:2403–2404.