Cancer Chemother Pharmacol (1989) 23 (Suppl): S 104–S 109

Cancer Chemotherapy and Pharmacology

Experience with transplantation in the treatment of liver cancer

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Summary. Thirteen patients with hepatic tumors, from the Boston Center for Liver Transplantation, have been transplanted among a total of 169 recipients. Ten were transplanted primarily for tumor, while three other patients harbored incidental tumors. Two perioperative deaths occurred (15%). Eight patients had hepatocellular carcinoma, one hepatoblastoma and four bile duct (Klatskin) tumors. Two of the bile duct cancers recurred with patient deaths at 9 and 10 months. The remaining nine patients are alive from between 1 month and 36 months postoperatively. A selected review of the literature allowed analysis of follow-up on 185 patients transplanted for tumor. Overall, the proportion of patients transplanted for tumor was 16%. Fifty-two percent of patients had hepatocellular carcinomas (HCC), 24% cholangiocarcinomas, 10% other primary liver tumors, and 14% metastatic hepatic tumors. Median survival for HCC was 1 year; 90-day mortality was 30%. Actuarial survival for 1, 2 and 3 years was 49%, 37% and 30% respectively. Fibrolamellar HCC and incidental HCC had significantly better results than other HCC. Tumor recurrence was present in 72% of autopsies after 90 days. Transplantation for HCC has satisfactory results in selected patients and may be improved by adjuvant chemotherapy. The median survival with cholangiocarcinomas was 8 months; 90-day mortality was 40%. Actuarial survival for 1 year was 36%. Recurrence was present in 100% of autopsies after 90 days. Survival after transplantation for this tumor was similar to that observed in patients not undergoing surgical treatment. Median survival for 18 other primary hepatic tumors was 16 months. Transplantation in carefully selected patients with these other primary tumors appears warranted. Although experience overall with transplantation for metastatic disease has been relatively unfavorable, each histological type must be considered independently.

Introduction

Even as advances in radiographic imaging and surgical technique have furthered attempts to resect neoplasms of the liver surgically, similar technological and immunological advances have spawned increasing efforts to identify appropriate patient populations amenable to curative treatment by liver transplantation. The magnitude of the problem is illustrated by observation that hepatocellular carcinoma is the most common malignancy in the world. The incidence varies worldwide with the highest incidence in African black and Oriental populations, and in areas endemic for hepatitis B. While relatively rare in the United States, often it is found coincidentally in the presence of cirrhosis secondary to hemochromatosis, chronic active hepatitis, α-1-antitrypsin deficiency, or alcohol.

A host of etiological agents have been associated with hepatocellular carcinoma, including hepatitis B virus, aflatoxin, alcohol, and hydrocarbons, stimulating efforts to reduce disease development by preventive management such as mass immunization (hepatitis B vaccine) of populations at risk. The historically low resectability rate for many of the hepatic malignant neoplasms has mandated a search for effective chemotherapeutic agents for the control of systemic disease. To date no standard chemotherapeutic regimens can provide satisfactory disease control, highlighting the importance of early detection and surgical extirpation.

With the introduction of cyclosporine and modifications in the technique of hepatic replacement, including the development of venous bypass, rising survival rates encouraged the proliferation of centers providing liver transplantation for patients with a wide variety of hepatic failure disorders [35]. Not unexpectedly, liver tumors represent an important group of liver disease states amenable to treatment by liver replacement. Although the mechanical aspects of hepatectomy are frequently less difficult than in many of the chronic cirrhotic disease states, the high incidence of tumor recurrence has encouraged scrutiny of the anticipated results of this complicated therapy. The critical scarcity of donor organs will continue to provide a major stimulus for optimal strategy in selection of appropriate patient and disease processes for management by liver transplantation.

In 1983 the N.I.H. sponsored a consensus development conference to analyze the results of liver transplantation for a broad spectrum of liver disease states including hepatic neoplasm [26]. Although Scharschmidt reported the multicenter experience in four major liver transplant programs, a considerable number of additional transplants for tumor have accrued since then [33].

Patients and methods

Patients from the Boston Center for Liver Transplantation (New England Deaconess Hospital, Massachusetts Gener-

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al Hospital, New England Medical Center, and Boston Children's Hospital) were identified who had hepatic malignancy at the time of transplantation. Clinical and follow-up data were abstracted from the central data registry located at the New England Organ Bank [18]. As a basis for assessing the application of hepatic transplantation for malignancy, additional reports from the literature, providing adequately detailed clinical information *and* follow-up data on *individual* patients, were selected for data analysis [5, 6, 9, 10, 12, 14, 16, 17, 21–34]. Patients were grouped by histological tumor type: hepatocellular carcinoma, cholangiocarcinoma (including Klatskin tumors), other primary hepatic tumors, and metastatic liver tumors. These combined data were then analyzed using standard statistical software (BMDP Statistical Software Inc., Los Angeles, Calif). Kaplan-Meier product limit analysis was used to calculate survival distributions. The significance of differences between survival distributions was determined by Mantel-Cox log-rank analysis. Survival data were expressed as the mean ± standard error of the mean.

Results

Out of 169 patients receiving 190 hepatic transplantations in Boston from July 1 1983 to November 1 1987, 13 patients with malignancy were identified. One patient with hepatoblastoma was aged 6 years and the remainder were adults. Ten were male, three female. Ten were transplanted with tumor as the indication while three hepatocellular carcinomas (HCC) were found coincidentally in cirrhotic livers transplanted for hepatic failure. Perioperative mortality was 15% (2 out of 13). Two patients with central cholangiocarcinomas (Klatskin) died from diffuse peritoneal recurrences at 9 and 10 months. Table 1 summarizes the pathology and survival of all 13 patients.

The 13 patients were combined with others from five reported series in the literature, identifying a total of 185 patients transplanted with hepatic tumors. The publication sources for these patients are shown in Table 2, together with the time period covered. Overall, 16% of patients from four centers were transplanted with malignant disease. The proportion transplanted for tumor has been declining with time at Pittsburgh [14]. Likewise, at Cambridge among the first 125 patients, 38 (30%) had cancer, whereas among the next 209 patients after July 1982, 40 (19%) had cancer [9, 10]. In Los Angeles, 8 (16%) of the first 50 patients had cancer, while after February 1 1986 only 2 (6%) of the next 33 patients had cancer [5, 6, 12]. In Boston, the proportion transplanted for cancer has always been relatively low. For all patients demonstrating malignancy in their resected specimen, known malignancy was the primary transplant indication in 76%, 77% and 70% of patients, respectively, at Pittsburgh, Boston and Los Angeles, while in the remaining patients, tumors were found coincidentally during pathological or radiographical examination of the native liver.

The distribution of histology of the audited patients is shown in Table 3. Ninety-seven (52%) out of 185 were hepatocellular carcinomas, 45 (24%) were either intrahepatic or extrahepatic (Klatskin) cholangiocarcinomas. Thirteen of these were Klatskin tumors at the hepatic bifurcation, eight from Pittsburgh, four from Boston and one from Los Angeles. Cases from Cambridge were not specified. Eighteen (10%) of patients had other types of primary hepatic

Table 1. Liver recipients with tumor

Pathology	Follow-up (months)	Status	Comments[a]
Hepatocellular	36	Alive	
	18	Alive	Incidental, CAH
	18	Alive	Incidental, CAH
	13	Alive	
	1	Alive	
	7 days	Alive	
	7 days	Dead	Rejection, autopsy NED
	1 day	Dead	Incidental, scl. cholang.
Hepatoblastoma	9	Alive	
Klatskin	36	Alive	Positive margin at op.
	13	Alive	
	10	Dead	Recurrence
	9	Dead	Recurrence

[a] CAH = chronic active hepatitis
Scl. cholang. = sclerosing cholangitis
NED = no evidence of disease

Table 2.

No. (%) patients with tumor	Total no. recipients	Center	Era	References
93 (28%)	334	1. Cambridge	1968–87	[9, 10]
54 (11%)	500	2. Pittsburgh	1963–85	[14, 17, 34]
13 (8%)	169	3. Boston	1983–87	Current
10 (12%)	83	4. Los Angeles	1984–86	[5, 6, 12]
10	[a]	5. Vienna	1982–86	[23]
5	[a]	6. Innsbruck	1982–85	[16, 21, 22]

[a] Two centers reporting metastatic results only

Table 3. Tumor types by center

Tumor type	Total		Center					
			1	2	3	4	5	6
Hepatocellular		97	48	37	8	4		
Fibrolamellar	7			7				
Incidental	18		1	12	3	2		
Cholangiocarcinoma[a]		45	30	10	4	1		
Other primary tumors		18						
Hepatoblastoma	3			1	1	1		
EHES[b]	5			3		2		
Angiosarcoma	6		5	1				
Other sarcoma	2		1	1				
Schwannoma	1					1		
Adenocarcinoma	1			1				
Metastatic tumors		25						
Colon	11		1				9	1
Breast	3							3
Leiomyosarcoma	2		1			1		
Apudoma	2		1				1	
Hypernephroma	1		1					
Pancreas	1		1					
Unknown	5		4					1
Total	185							

[a] Intrahepatic and extrahepatic
[b] Epithelioid hemangioendothelial sarcoma

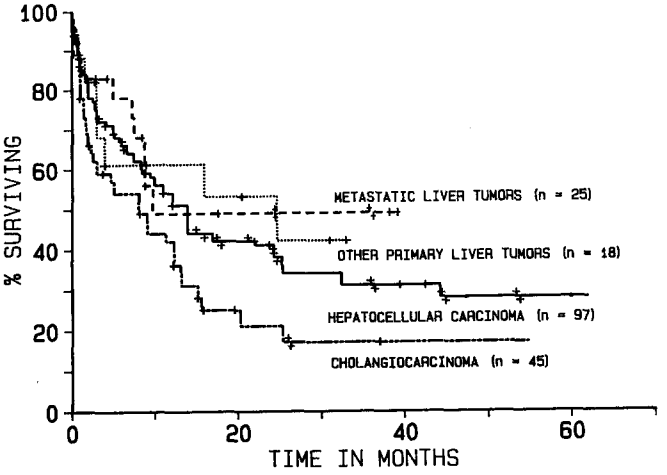

Fig. 1. Survival as a function of hepatic tumor type. All observations are included. Each hatch mark on the curves represents a patient who withdrew from follow-up study alive. Standard error of the cumulative proportion surviving is between 0.02 and 0.11 for all points on each curve with ten or more patients remaining at risk. There are no significant differences between curves

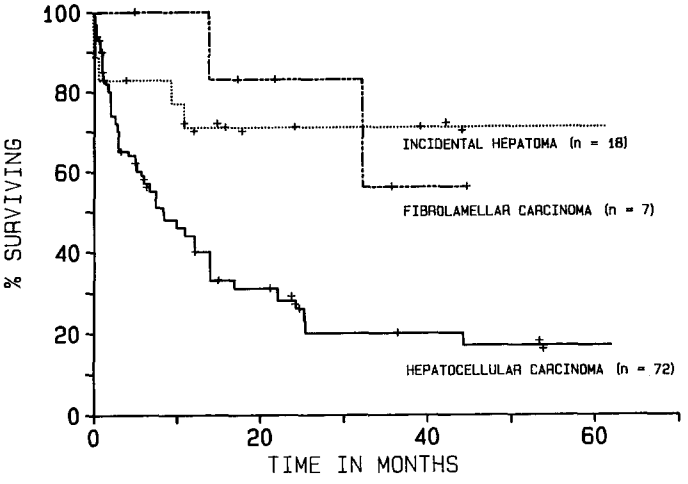

Fig. 2. Survival for patients with hepatocellular carcinoma as a function of indication for surgery and histological subtype. All observations are included. Each hatch mark represents a patient who withdrew from follow-up study alive. Standard error of the cummulative proportion surviving is between 0.02 and 0.11 for all points of the curves with ten or more patients remaining at risk. There is a statistical survival difference between hepatocellular carcinomas resected incidentally versus those resected for tumor ($P < 0.05$) as well as between fibrolamellar variants and the other hepatocellular carcinomas ($P < 0.025$). There was no significant difference between the upper two curves

tumors. Finally, 25 (14%) of patients had metastatic tumors from a wide spectrum of original primaries.

All survival observations for patients with hepatocellular carcinomas, cholangiocarcinomas, other primary hepatic tumors, and metastatic tumors are shown in Fig. 1. Median survival for 97 hepatocellular carcinomas was 1 year. Ninety-day mortality was 29 (30%) out of 97. Actuarial survival for 1, 2 and 3 years is $49 \pm 5\%$, $37 \pm 6\%$, and $30 \pm 6\%$. Too few patients remain to make statements of survival valid beyond these intervals. As shown in Fig. 2, survival for fibrolamellar HCC and for patients resected with incidental hepatomas is significantly better than for other variants of HCC ($P < .05$). The 1- and 2-year actuarial survival for the former groups is more than $70 \pm 11\%$, while for the other variants of hepatoma, it is $38 \pm 6\%$ and $24 \pm 6\%$ respectively.

Of 33 patients with hepatocellular carcinoma alive after 90 days but dying thereafter, the cause of death was known for 29 of them. In 21 cases (72%) it was due to recurrent tumor while in the remaining 8 it was due to other transplantation-related causes.

The median survival for 45 patients with cholangiocarcinoma was 8 months. The early mortality rate (90 days) was 18 (40%) out of 45, and 1-year survival was $36 \pm 8\%$. Although this survival curve appears worse than for hepatocellular carcinoma, the difference does not achieve significance ($P = 0.06$). Of 16 patients who died after 90 days, the cause of death was known for 12 of them. All 12 (100%) died with tumor recurrence.

The median survival for 18 other primary hepatic tumors, taken as a group, was 16 months. It is most appropriate to discuss each type individually. Of the patients with hepatoblastomas, all three were alive without evidence of recurrence at 9 months, 33 months, and 7 years 2 months. Of the five patients with epitheloid hemangioendothelial sarcomas, three were alive at more than 1 month, 20.5 months, and 31 months, and two were dead with recurrence at 3 months and 16 months. Of six patients with angiosarcomas, three died of pneumonia or liver failure at 4 days, 25 days and 49 days, one died at 2 years (cause unknown) and one was alive at 84 days. Of two unspecified sarcoma cases, one died at day 0 and the other of unknown type is alive at 8 years 8 months. A patient with schwannoma died at 4 months with recurrence while one patient with adenocarcinoma of undetermined origin was alive at 4 months.

The median survival for 25 collected patients with various metastatic tumors was 10 months. For eleven patients with colon cancers, three died at 0, 7 and 7 days, two died with recurrence at 5 and 10 months, six were alive at 1 month, 2 months, 3 months, 18 months with recurrence, 37 months and 39 months with recurrence. Thus four (80%) out of five patients living longer than 90 days have had recurrence of tumor. Of two with metastatic leiomyosarcoma, one died at 3 days and the other was alive at 3 years. The results of cases of metastatic breast carcinoma are well discussed elsewhere [16, 21, 22] although all were alive with recurrence at 9–40 months. Of two patients with apudomas, one was alive at 2 years and another with pheochromocytoma was alive at 9 months. A patient with pancreatic carcinoma was dead at 37 days with recurrence, and the one recipient with hypernephroma died at 9 months with recurrence.

Discussion

The natural history of hepatocellular carcinoma (HCC) is bleak, with multiple series reviewed in 1977 by Foster and Berman showing almost all patients dead within a few months. However, a few patients, with apparently favorable histology, lived for a few years [15]. A more recent series in the United States of 67 untreated patients from the Mayo Clinic showed a median survival of five weeks [1], and one from Japan of 169 untreated patients at Chiba University showed a median survival of 1.6 months [27].

Rates of resection cited in Foster and Berman's review have varied from 9% to 37%. Overall, 12% of 2202 collected patients were resected. However, extrahepatic metastases were present in only 52% of 748 patients autopsied after death from HCC [15], indicating that higher resection rates should be possible.

The collective operative mortality for HCC resection was 21%. Actuarial survival figures of 1–5 years for 101 patients resected for HCC respectively were respectively 80%, 68%, 53%, 37%, and 30%. Survival was influenced very negatively by the presence of cirrhosis. Western patients have fared better than Asian patients, a finding probably related to the relative incidence of cirrhosis. Foster and Berman state that conventional resection of HCC should not be performed in the cirrhotic patient. The actual size of the tumor did not relate to survival. Multiple nodules versus solitary nodules also did not relate to survival [15]. In 46 patients at the Mayo Clinic resected for HCC, 3-, 5-, and 10-year survival was 65%, 36%, and 33% respectively [1]. In 98 resected patients from Chiba University, 1-, 2- and 3-year survival was 65%, 43% and 34% respectively [27].

In evaluating data on adjuvant therapy for HCC, the lack of objective criteria for tumor response and the variation among reports is a serious problem. However, recent reviews [7, 20] do identify the best studied and most reliable agents found to date. 5-Fluorodeoxyuridine has demonstrated response rates of 55%–75% in four separate reports. 5-Fluorodeoxyuridine has been reported to prolong median survival, achieve symptomatic improvements, and significantly prolong life [8]. It has been recommended that this agent be administered by continuous regional infusion for 5 days or longer. Intra-arterial doxorubicin has also been shown to have substantial response rates. An analogue, epidoxorubicin, may well reduce untoward cardiac side-effects while maintaining good response rates. Other agents and combinations of agents have not been sufficiently evaluated to recommend for HCC at this time. External beam radiotherapy and intraoperative radiotherapy have not been shown to be of benefit. The use of radio-labeled antibodies, such as ^{131}I-antiferritin, may have important benefit, but so far this has been shown in only a few patients with long-term remissions [28].

For HCC treated by transplantation, we found 1-, 2- and 3-year survival to be 49%, 37% and 30% respectively, figures that approach the less complex standard resections and are especially noteworthy given the 90-day mortality of 30%. Patients with fibrolamellar HCC and incidental HCC have survival rates almost double those of other HCC patients. Recurrence of tumor was noted in 72% of patients succumbing after 90 days.

In a recent report, Pichlmayr reported upon 49 patients with HCC, transplanted with a 60-day mortality of 15% and 2-year survival of 60%. Survival was better among 21 patients without cirrhosis than in 28 patients with cirrhosis [29].

Recurrence rates after transplant for HCC have been 57%–60% in two large series [14, 17, 32]. Recurrences have been located predominantly in the lung and the grafted liver and, to a lesser extent, in the peritoneum, bone and brain [14, 17, 30]. The high recurrence rates may be caused by the advanced stage of the disease process at the time of transplant. The relatively lower recurrence rate and longer survival of patients with HCC resected incidentally to cirrhosis verify this point. Secondly, invasion of the portal vein and inferior vena cava may contribute to recurrence. In 232 cases of HCC, the portal vein was involved in 65% and the hepatic veins in 23% [25]. Foster and Berman noted the poor outcome in patients with vascular invasion who underwent standard resection [15]. Recurrence may be hastened by required immunosuppression [14, 22]. Clearly, known extrahepatic nodal spread portends a poor outcome [3] and a lack of lymph node involvement portends a better outcome with recent reports of 70% and 50% survival at 2 and 5 years, respectively, under these circumstances [29]. In many of the early deaths in the 185 cases reviewed here, known extrahepatic metastases existed and contributed to poor survival.

The biology of the tumor as an influence on outcome is demonstrated by the so-called fibrolamellar variant, which has recurred more slowly after transplant than the usual HCC. For the usual HCC, recurrence is reported after orthotopic liver transplantation from 4 months to 12 months postoperatively with a mean of 6 months, while for fibrolamellar variants, recurrence is reported from 13 months to 30 months with a mean of 20 months [14]. This relatively indolent course has also been noted after partial resections [13, 24, 34].

Patients with HCC should be considered candidates for transplant if they have cirrhosis precluding partial hepatectomy or large tumors involving parenchyma, such that even extended hepatic resections cannot encompass all the tumor. Evaluation should include upper gastrointestinal series, barium enema, mammograms, or other such studies as are necessary to rule out other primary tumor. Computed tomography scans of the chest and abdomen and a bone scan should rule out gross metastases. Doppler ultrasound, supplemented with arteriography as necessary, can assess portal vein patency and identify the extent of involvement of the portal and/or hepatic veins with tumor. Data would suggest that patients should then receive continuous regional infusion of 5-fluorodeoxyuridine and/or epidoxorubicin preoperatively. For large tumors of the non-fibrolamellar types, better results may be obtained if only those patients who respond by decreased tumor volumetrics, using computed tomography reconstruction, are considered. These patients, having demonstrated sensitivity of the cell line to the adjuvant therapy, may be expected to respond best to postoperative continuation of the adjuvant agents. It is hoped that this will lead to lower metastatic recurrence rates in the lung, liver graft and elsewhere. At the time of anticipated transplant, a back-up patient should be available and the candidate explored with biopsy of periportal and celiac lymph nodes to rule out extrahepatic disease. During the course of the operation, if circumstances allow, all celiac, hepatic and portal lymphatic tissue should be skeletonized. The portal vein should be resected almost to the pancreas with a relatively long donor portal vein reconstruction. Likewise, the hepatic artery should be taken near the junction with the gastroduodenal artery or, if adjacent tissues are suspicious, sacrificed at the celic axis, with arterial reconstruction using a donor iliac artery conduit. The suprahepatic cuff should be as short as is technically feasible, even to the extent of obtaining intrapericardial control. The bile duct should be resected behind the duodenum and biliary reconstruction via a Roux-en-Y choledocojejunostomy. Postoperatively, patients should be considered for continued

5-fluorodeoxyuridine infusions. In addition to serial examinations, they should receive chest radiographs and abdominal and chest computed tomography scans every 3 months.

Although bile duct tumors are not common, proximal tumors represent about 53% of the total. With no treatment or palliative stenting, survival was 0.5 year and 1.6 years respectively [4]. Without resection, 1-, 3- and 5-year survival figures of respectively 32%, 3% and 0% have been reported [31]. Resection rates of 10%–37% have been reported [2, 12]. Operative mortality has been reported in 4%–15% of cases [4, 31]. Median survival in 9 patients after hepatectomy for cholangiocarcinoma and in 16 patients after skeletomization resection of Klatskin tumors was 2.3 years with 1-, 3- and 5-year survival figures of 84%, 44% and 35%, although recurrence was 100% [31]. The observation that more than half of the patients who fail after major resectional treatment demonstrate recurrence limited to the local regional area suggests a possible role for more aggressive local regional therapy, possibly as a combination of intraoperative and external-beam radiation [19]. To date, however, no proven benefit from chemotherapy or radiotherapy has been shown for this tumor.

The experience reported here in 45 patients undergoing transplantation for cholangiocarcinoma reveals a median survival of 8 months and 1-year survival of 36%. This is discouraging as it is no better than survival for patients with cholangiocarcinoma receiving no treatment. Without advances in adjuvant chemotherapy or radiotherapy, transplantation for patients with cholangiocarcinoma cannot be advocated unless it is performed as part of an investigational protocol.

As a group, the 16 patients with other types of primary hepatic cancer have demonstrated a median survival after transplantation of 16 months. Although small in number, particularly encouraging results are noted here with hepatoblastomas. At this time, it seems appropriate to continue to transplant carefully selected patients who have other primary hepatic tumors with historically favorable biological behavior not amenable to standard resections in the absence of extrahepatic disease.

Metastatic disease was noted in 25 collected patients undergoing transplantation with a median survival of 10 months. Although some authors are encouraged by their experiences, most are discouraged from further trials [21]. Pichlmayer recently reported 1-year survival after transplantation for metastatic cancer of 5% [29]. At our institution, we have not transplanted any patient for metastatic disease and do not feel that this is currently indicated, except possibly for slow-growing, hormonally active apudomas and sarcomas, until improved adjuvant therapy becomes available.

Acknowledgements. The authors would like to acknowledge the assistance of Dr. Benjamin Cosimi (Massachusetts General Hospital) and Dr. Sang Cho (New England Medical Center Hospital) for providing information on their recipients with liver tumors. The authors would also like to acknowledge the expertise of Dr. Mark Roberts for the statistical analyses performed.

References

1. Adson MA, Farnell MB (1981) Hepatobiliary cancer – surgical considerations. Mayo Clinic Proc 56: 686
2. Alexander F, Rossi RL, O'Bryan M, et al. (1984) Biliary carcinoma. A review of 109 cases. Am J Surg 147: 503
3. Angrisani L, Jurewicz WA, Clements DG, et al. (1986) Liver transplantation for liver cancer. Transplant Proc 18: 1218
4. Broe PJ, Cameron JL (1981) The management of proximal biliary tract tumors. Adv Surg 15: 47
5. Busuttil RW, Memsic LD, Quinones-Baldrich W, et al. (1986) Liver transplantation at UCLA. Program development, organization, initiation and early results. Am J Surg 152: 75
6. Busuttil RW, Colonna JO, Hiatt JR, et al. (1987) The first 100 liver transplants at UCLA. Ann Surg 206: 387
7. Cady B (1987) Infusional therapy of hepatoma: current results. In Hepatic and biliary cancer. Marcel Dekker, Inc, New York, p 255
8. Cady B, Oberfield RA (1974) Arterial infusion chemotherapy of hepatoma. Surg Gynecol Obstet 138: 381
9. Calne RY (1983) Liver transplantation. Grune and Stratton, New York, p 378
10. Calne RY (1987) Liver transplantation, 2nd edn. Grune and Stratton, New York, p 542
11. Cameron JL, Broe P, Zuidema GD (1987) Proximal bile duct tumors: surgical management with silastic transhepatic biliary stents. Ann Surg 196: 412
12. Colonna JO, Ray RA, Goldstein LI, et al. (1986) Orthotopic liver transplantation for hepatobiliary malignancy. Report of three cases of special interest. Transplantation 42: 561
13. Craig JR, Peters RL, Edmondson HA, Omata M (1980) Fibrolamellar carcinoma of the liver. Cancer 46: 372
14. Esquivel CO, Iwatsuki S, Gordon RD, Starzl TE (1987) Transplantation for primary liver cancer. In Hepatic and biliary cancer. Marcel Dekker Inc., New York, p 477
15. Foster JH, Berman MM (1977) Solid liver tumors. W. B. Saunders Co., Philadelphia, p 1
16. Huber C, Niederwieser D, Schonitzer D, et al. (1984) Liver transplantation followed by high-dose cyclophosphamide, total-body irradiation, and autologous bone marrow transplantation for treatment of metastatic breast cancer. A case report. Transplantation 37: 311
17. Iwatsuki S, Gordon RD, Shaw BW, Starzl TE (1985) Role of liver transplantation in cancer therapy. Ann Surg 202: 401
18. Jenkins RL (1986) The Boston Center for Liver Transplantation (BCLT): initial experience of a new surgical consortium. Arch Surg 121: 424
19. Kopelson G, Galdabini J, Warshaw A, Gunderson LL (1981) Patterns of failure after curative surgery for extrahepatic biliary tract carcinoma: implications for adjuvant therapy. Int J Radiat Oncol Biol Phys 7: 413
20. Lokich J (1987) Chemotherapy for hepatoma. In Hepatic and biliary cancer. Marcel Dekker Inc, New York, p 239
21. Margreiter R, Huber C, Neiderwieser D, et al. (1985) Combined bone marrow and liver transplantation with total body irradiation and high dose cyclophosphamide in the treatment of metastatic liver disease. Transplant Proc 17: 296
22. Margreiter R (1986) Indications for liver transplantation for primary and secondary liver tumors. Transplant Proc 18: 74
23. Muhlbacher F, Piza F (1987) Orthotopic liver transplantation for secondary malignancies of the liver. Transplant Proc 19: 2396
24. Nagorney DM, Adson MA, Weiland LH, et al. (1985) Fibrolamellar hepatoma. Am J Surg 149: 113
25. Nakashima T, Okuda K, Kojiro M, et al. (1983) Pathology of hepatocellular carcinoma in Japan – 232 consecutive cases autopsied in 10 years. Cancer 51: 867
26. National Institutes of Health Consensus Development Conference on Liver Transplantation (1984) Hepatology 4, suppl. 1 S
27. Okuda K, Obata H, Nakajima Y, et al. (1984) Prognosis of primary hepatocellular carcinoma. Hepatology 4, suppl. 1: 39
28. Order SE (1987) New radiotherapeutic approaches to hepatoma. In Hepatic and biliary cancer. Marcel Dekker Inc. New York, p 267

29. Pichlmayr R (1988) Is there a place for liver grafting for malignancy? Transplant Proc. 20 (1 Suppl. 1): 478
30. Pichlmayr R, Brolsch C, Wonigeit K, et al. (1984) Experiences with liver transplantations in Hannover. Hepatology 4, suppl. 1: 569
31. Pinson CW, Rossi RL (1988) Extended right hepatic lobectomy, left hepatic lobectomy, and skeletonization resection for proximal bile duct cancer. World J Surg 12: 52
32. Rolles K, Williams R, Neuberger J, Calne R (1984) The Cambridge and King's College Hospital Experience of liver transplantation, 1968–1983. Hepatology 4, suppl. 1: 509
33. Scharschmidt BF (1984) Human liver transplantation: analysis of data on 540 patients from 4 centers. Hepatology 4, suppl. 1: 955
34. Starzl TE, Iwatsuki S, Shaw BW, et al. (1986) Treatment of fibrolamellar hepatoma with partial or total hepatectomy and transplantation of the liver. Surg Gynecol Obstet 162: 145
35. Starzl TE, Iwatsuki S, Van-Thiel DH, et al. (1986) Evolution of liver transplantation. Hepatology 2: 614