25

Transplantation for Primary Liver Cancer

CARLOS O. ESQUIVEL, SHUNZABURO IWATSUKI, ROBERT D. GORDON, and THOMAS E. STARZL
University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania

Treatment of primary carcinoma of the liver constitutes a challenge to the physician, and despite aggressive treatment, the prognosis is poor. The resection rate for primary liver malignancy ranges from 15 to 30% in several studies. Although there has been an increase in the resection rate because of improvements in surgical techniques and postoperative care, the overall prognosis remains grim [11]. It was in the presence of such discouraging facts that liver transplantation was undertaken as the only hope in patients with unresectable lesions.

The experience with orthotopic liver transplantation in 55 patients with primary hepatic malignancy is the basis of this chapter. An update will be provided of a recent report on the same subject [7].

I. CLINICAL FEATURES

From March 1, 1963, to August 1, 1985, 575 patients received orthotopic liver transplantations for several hepatic diseases. Treatment was performed at the University of Colorado Health Sciences Center until the end of 1980, and during that period of time, the immunosuppression mostly consisted of azathioprine, antilymphocyte globulin (ALG), and steroids. Since 1981, treatment has been provided at the University of Pittsburgh Health Center and the immunosuppression has consisted of cyclosporine and steroids.

Supported by Research Grants from the Veterans Administration and Project Grant No. AM-29961 from the National Institutes of Health, Bethesda, Maryland.

Table 1 Number of Patients Receiving Orthotopic Liver Transplantation in the Presence of Primary Hepatic Malignancy

Year	Total no. transplants	No. patients with primary malignancy	%
1963	5	4	80
1966	1	1	100
1967	6	1	16.6
1968	12	4	33.3
1969	6	2	33.3
1970	10	1	10
1971	11	1	9.1
1972	11	0	–
1973	13	0	–
1974	20	4	20
1975	9	1	11.1
1976	14	2	14.3
1977	21	1	4.8
1978	19	1	5.3
1979	12	1	8.3
1980	14	2	14.3
1981	26	5	19.2
1982	62	6	9.7
1983	76	8	10.5
1984	135	10	7.4
1985	132[a]	1	0.8

[a]Until August 1, 1985.

A total of 55 patients (9.6%) received orthotopic liver transplants in the presence of primary hepatic malignancy, with the annual distribution shown in Table 1. There were 32 females and 23 males, and their ages ranged from 2 to 68 years, with a mean of 30. Table 2 lists the histological types of primary liver cancer found in this series. The most common malignancy encountered was hepatocellular carcinoma, which was present in 38 patients (69%); 7 of the 38 had the fibrolamellar variant. The other tumors were 8 bile duct carcinomas (Klatskin tumors), 3 epithelioid hemangioendothelial sarcomas, 2 cholangiocarcinomas, and 1 each hepatoblastoma, angiosarcoma, adenocarcinoma of unknown primary, and sarcoma of undetermined cell type.

Table 2 Histological Diagnosis of Primary Liver Cancers in Patients Treated with Orthotopic Liver Transplants

Diagnosis	Male	Female	Total (%)
Hepatocellular carcinoma	16	22	38 (69)
Bile duct carcinoma (Klatskin tumor)	5	3	8 (14.5)
Epitheloid hemangioendothelial sarcoma	0	3	3 (5.5)
Cholangiocarcinoma	1	1	2 (3.6)
Hepatoblastoma	0	1	1 (1.8)
Hemangiosarcoma	0	1	1 (1.8)
Sarcoma (unclassified)	0	1	1 (1.8)
Adenocarcinoma (unknown primary)	0	1	1 (1.8)

A total of 42 patients (76%) were known to have unresectable lesions and received liver transplants as the principal method of therapy. For didactic purposes, this group of patients will be referred to as "unresectable malignancy." The first 20 patients were treated with azathioprine, prednisone, and anti-lymphocyte globulin; the rest were treated with cyclosporine and prednisone.

A total of 13 patients (24%) received transplants for nonneoplastic end-stage liver disease and were found to have coincidental primary liver malignancy. This group will be referred to as "incidental malignancy." Of these patients, 3 were treated with azathioprine, prednisone, and ALG, and 10 were treated with cyclosporine and prednisone.

II. UNRESECTABLE MALIGNANCY

Preoperative evaluation for extrahepatic involvement was negative in this group of patients; however, 3 patients had metastatic disease at the time of transplantation and were left with gross residual neoplasm. A 27-year-old man with sarcoma of undetermined cell type was found to have fine metastatic lesions in the peritoneal cavity and lungs at the time of transplantation; nevertheless, this patients is still alive at this writing with no evidence of metastatic disease over a 9-year period. The second patient was a 35-year-old female who was found to have metastases to the lungs and peritoneum during the surgical intervention. This patient died 3 months later, and in addition, the autopsy revealed metastases to the bone marrow. The third patient was a 54-year-old female who was noted to have metastatic involvement in the regional lymph nodes. After some controversy, the tumor was classified as an adenocarcinoma of unknown primary. This patient, who received two courses of doxorubicin hydrochloride (adriamycin) and vincristine (Oncovin and

Table 3 Coexistent Liver Disease in Patients with Unresectable Primary Hepatic Malignancies

Coexistent disease	N = patients (%)	Age (years)
Immunosuppression with azathioprine + prednisone + ALG (N = 20)		
Postnecrotic cirrhosis	4 (20)	29, 43, 48, 52
Biliary atresia	1 (5)	11
Tyrosinemia	1 (5)	9
Immunosuppression with cyclosporine + prednisone (N = 22)		
Postnecrotic cirrhosis	2 (9)	51, 53
Sclerosing cholangitis	1 (4.5)	33
Thorotrast liver	1 (4.5)	52
Tyrosinemia	1 (4.5)	5

a course of 5-fluorouracil, cyclosphosphamide (Cytoxan) and methotrexate preoperatively, is alive with no evidence of tumor spread over a 10-month period.

A total of 6 patients during the azathioprine and 1 during the cyclosporine periods died of various complications of liver transplantation within 1 month of the operation. A single patient had evidence of extrahepatic tumor involvement at the autopsy. This patient was a 52-year-old male with a cholangiocarcinoma who died on postoperative day 5 of graft failure, sepsis, and pulmonary embolism. The postmortem examination revealed metastases to the bone, lungs, kidney, and lymph nodes.

A list of coexistent liver diseases in some of these patients is given in Table 3, but they had no effect in the final outcome.

A. Azathioprine Era

1. Recurrence

Omitting 6 patients who died postoperatively, 14 patients survived at least 2 months and thus became available for meaningful observation about recurrence (Table 4).

The recurrence rate was 64%. In patients with hepatocellular carcinoma, including the patient with the fibrolamellar tumor, the recurrence rate was 66%. The malignancy recurred from 2 to 13 months, with a mean of 4 months. The patient with the fibrolamellar variant had the longest tumor-free interval, which was 13 months. All these patients died of carcinomatosis, and the most common organs involved were the allograft and lungs.

Table 4 Liver Transplantation in Patients with Unresectable Primary Liver Carcinoma During Azathioprine + Prednisone Period

Histology	No. patients	Recurrence (%)	No. survivors (%)
Hepatocellular carcinoma	8	5 (62.5)	0 (0)
Fibrolamellar variant	1	1 (100)	
Bile duct cancer (Klatskin tumor)	3	2 (66)	0 (0)
Epitheloid hemangioendothelial sarcoma	1	1 (100)	0 (0)
Sarcoma of undetermined cell type	1[a]	0 (0)	1 (100)

[a]Patient had intra-abdominal and pulmonary metastases at transplantation.

Of 3 patients with bile duct carcinoma, 2 had recurrence at 21 and 42 months, respectively. The organs involved were the allograft and bile duct and were the cause of the patients' demise.

2. Survival

There has been only 1 survivor in the azathioprine group. This patient, previously mentioned, had a sarcoma of undetermined cell type with metastases at the time of transplantation; however, he is alive and free of disease 9 years later. A total of 9 patients (64%) died of recurrent disease. The remaining 4 patients died of various infections at 2, 2, 3, and 6 months, respectively. The postmortem examinations revealed no residual tumor. Of the 20 patients, 35% survived 6 months and 30% survived 1 year, of whom all but 1 subsequently died.

B. Cyclosporine Era

1. Recurrence

In the cyclosporine era, only 1 patient died within 1 month of the operation of sepsis and graft failure. The autopsy disclosed no residual neoplasm.

The recurrence rate according to the type of malignancy in the remaining 21 patients is shown in Table 5. The recurrence rate was 58%, excluding the 2 patients who were left with gross tumor at the time of the operation. The incidence of recurrence was 50% in patients with hepatocellular carcinoma and 50% in patients with the fibrolamellar variant. All non-fibrolamellar hepatocellular carcinomas recurred within 1 year, from 4 to 12 months with a mean of 6 months, whereas the fibrolamellar type recurred after 1 year, from 13 to 30 months with a mean of 20 months. The 2 patients with bile duct carcinoma (Klatskin tumor) and another patient with cholangiocarcinoma had recurrent disease at 6, 10, and 15 months,

Table 5 Liver Transplantation in Patients with Unresectable Primary Liver Carcinoma During Cyclosporine and Prednisone Period

Histology	No. patients	Recurrence (%)	No. survivors (%)
Hepatocellular carcinoma	8	4 (50)	3 (37.5)[a]
Fibrolamellar	6	3 (50)	4 (66)[b]
Bile duct carcinoma	2	2	0 (0)
Cholangiocarcinoma	1	1	0 (0)
Epitheloid hemangiosarcoma	2	1 (50)	1 (50)

[a]One patient had metastatic disease.
[b]Two patients have metastatic disease.

respectively. The most common organs involved were the liver and lungs. Occasional metastases to bone and brain were also observed.

2. Survival

The 6-month actuarial survival is 82%, reflecting the much improved recovery with cyclosporine therapy [15]; however, there is a decline in survival thereafter, chiefly from recurrence of malignancy, as shown in Table 5. At this writing, there are only 9 patients alive of the original 22 (41%) from 4 months to 48 months with a mean of approximately 23 months, but 1 of these survivors is a patient who had involvement of regional lymph nodes, and there are 3 others with known recurrences of hepatocellular carcinoma. Of the 14 patients with hepatocellular carcinoma, including the fibrolamellar variant, 4 are tumor free from 4 months to 4 years. In this particular group, the 2 longest survivors (27 and 48 months) had fibrolamellar hepatocellular carcinoma.

Death in patients with recurrent disease was directly related to the presence of malignancy. The causes of death in 4 other patients who died at 1, 2, 2, and 13 months were graft failure, ischemic necrosis of the colon, *Candida* sepsis, and liver dysfunction following retransplantation, respectively.

III. INCIDENTAL MALIGNANCY

There are 13 patients who received liver transplants for end-stage non-neoplastic liver disease and whose livers were found to contain incidental primary malignancies (Table 6). Ages ranged from 2 to 52 years with a mean of 16 years. Tumors could have been totally removed by partial hepatectomy if the liver had not been so seriously diseased. Of the 3 patients who belong to the azathioprine period, 1

Table 6 Liver Transplantation in Patients with Incidental Primary Liver Carcinoma

Histology	No. patients	Recurrence (%)	No. survivors (%)
Hepatocellular carcinoma	11	0 (0)	11 (100)
Hepatoblastoma	1	0 (0)	1 (100)

died on the first postoperative day. Hepatocellular carcinoma was found in 12 patients and a hepatoblastoma in 1 patient. Of the 13 patients, 12 are alive and free of recurrence (Table 6) from 10 months to more than 15 years. Table 7 lists the liver diseases for which liver transplantation was performed.

IV. GENERAL COMMENTS AND CONCLUSIONS

Primary hepatic malignancy, particularly hepatocellular carcinoma, carries a bleak prognosis. Many patients were diagnosed when the extension of the disease was such that treatment by conventional partial hepatectomy was not possible, leading to the early trials in liver transplantation [3,8,13,14]. The interest for this type of therapy persists because an effective alternative method of treatment is lacking and because the overall survival rate has improved in recent years with the introduction of cyclosporine and new surgical techniques [15].

The overall recurrence rate was high since almost two-thirds of the patients with unresectable lesions and who survived at least 2 months developed metastatic disease. Hepatocellular carcinoma is one of the most malignant neoplasms in terms of prognosis as became evident in this series, in which a 57% recurrent rate was observed. The nonfibrolamellar hepatocellular carcinoma recurred within 1 year of the operation, leading to a prompt death of the patients. Several factors may be

Table 7 Coexistent Disease in Patients with Incidental Primary Liver Carcinoma

Disease	No. patients	Age (years)
Biliary atresia	3	3, 7, 8
Tyrosinemia	4	2, 3, 3, 21
α_1-Antitrypsin deficiency	2	5, 47
Alagille's syndrome	1	9
Alcoholic cirrhosis	1	52
Cirrhosis, HBsAg-positive	1	45
Sea-blue histiocyte syndrome	1	7

implicated in this high recurrence rate. First, the extent of the disease may be too advanced by the time the patients received the transplants. Second, hepatocellular carcinoma is an aggressive cancer that invades vascular structures early [11]. Tumor thrombi in the portal vein and its branches are not an unusual occurrence in advanced hepatocellular carcinomas. In a series of 232 cases in Japan, Nakashima et al. reported portal vein invasion in 64.7% and in the major hepatic veins in 23.2%. Moreover, extrahepatic metastases may be spread via blood vessels or lymphatics or by continuity in the abdominal cavity [10]. Third, immunosuppression may enhance the growth of residual nest cells, as was suggested years ago [14] and supported recently in several investigations [1,6,9].

The fibrolamellar hepatic carcinoma is an exception. This tumor, which was originally described by Edmunson [5] and Peters [12], is known to be less aggressive than other primary hepatic carcinomas [2,4,16]. Although the recurrence rate was similar to that of the common hepatocellular carcinoma, the metastases appeared later and grew relatively slowly. In fact, one of the patients is still alive and well 2 years after the development of pulmonary metastases. Because of these characteristics, patients with this particular tumor appear to benefit from liver transplantation.

The prognosis with bile duct carcinoma (Klatskin tumor), cholangiocarcinoma, and sarcoma was very poor. Nonetheless, an occasional patient has had complete arrest and control of the malignant process. These results suggest that liver transplantation alone is not sufficient to control primary liver cancer, perhaps with the exception of the fibrolamellar carcinoma. However, chemotherapy may not be effective enough, since recently 2 patients who had nonfibrolamellar hepatocellular carcinoma and received aggressive treatment with adriamycin and other chemotherapeutic agents developed metastases within a few months; nevertheless, controlled prospective studies are certainly in order.

The striking aspect of this experience was the absence of recurrence in patients who were found to have an incidental primary hepatic carcinoma; therefore, the presence of hepatic malignancy appears not to be an absolute contraindication to liver transplantation.

V. SUMMARY

Orthotopic liver transplantation in patients with primary liver malignancy is reviewed. The recurrence rate was high in patients with unresectable cancer regardless of the histological diagnosis, leading to a prompt death of the patients. The only exception is the fibrolamellar variant of hepatocellular carcinoma in which, despite a recurrent rate of 57%, the metastases occurred late and grew slowly. Of the 42 patients with unresectable malignancy, only 10 patients are alive; however, 1 patient was left with residual cancer involving the regional lymph nodes and 3

others have metastases. Therefore, only 6 (14%) are possibly free of malignancy from 4 months to 9 years.

The encouraging aspect of this experience is that patients who had liver replacements for nonneoplastic end-stage liver disease and were found to have incidental malignancy have had no recurrence; therefore, the mere presence of a primary liver carcinoma is not an absolute contraindication for liver transplantation.

REFERENCES

1. Alexander, P., and Eccles, S. A. Host mediated mechanisms in the elimination of circulating cancer cells. Symp. Fundam. Cancer Res. 36:309-320, 1983.
2. Berman, M. M., Libbey, N. P., and Foster, J. H. Hepatocellular carcinoma: Polygonal cell type with fibrous stroma—an atypical variant with a favorable prognosis. Cancer 46:1448-1455, 1980.
3. Calne, R. Y. Liver Transplantation. In: *The Cambridge and King's College Hospital Experience*, edited by R. Y. Calne. Grune and Stratton, London, 1983, pp. 306-311.
4. Craig, J. R., Peters, R. L., Edmonson, H. A., and Omata, M. Fibrolamellar carcinoma of the liver: A tumor of adolescents and young adults with distinctive clinicopathologic features. Cancer 46:372-379, 1980.
5. Edmonson, H. A. Differential diagnosis of tumors and tumor-like lesions of the liver in infancy and childhood. Am. J. Dis. Child. 91:168-186, 1956.
6. Hanna, H. Role of natural killer cells in host defense against cancer metastasis. Symp. Fundam. Cancer Res. 36:309-320, 1983.
7. Iwatsuki, S., Gordon, R. D., Shaw, B. W., Jr., and Starzl, T. E. Role of liver transplantation in cancer therapy. Ann. Surg. (In press, 1985).
8. Iwatsuki, S., Klintmalm, G. B. G., and Starzl, T. E. Total hepatectomy and liver replacement (orthotopic liver transplantation) for primary hepatic malignancy. World J. Surg. 6(1):81-85, 1982.
9. Milas, L., and Peters, T. J. Conditioning of tissues for metastasis formation by radiation and cytotoxic drugs. Symp. Fundam. Cancer Res. 36:321-336, 1983.
10. Nakashima, T., Okuda, K., Kojiro, M., Yamaguchi, R., Sakamoto, K., and Ikara, T. Pathology of hepatocellular carcinoma in Japan—232 consecutive cases autopsied in 10 years. Cancer 51:867-877, 1983.
11. Okuda, K., and Nakashima, T. Primary carcinomas of the liver. In *Bockus Gastroenterology*, Vol. 5, edited by J. E. Berk. W. B. Saunders, Philadelphia, 1985, pp. 3315-3376.
12. Peters, R. L. Pathology of hepatocellular carcinoma. In *Hepatocellular Carcinoma*, edited by K. Okuda and R. L. Peters. Wiley, New York, 1975, pp. 107-168.
13. Pichlmayr, R., Brolsch, C. H., Wonigiet, K., Neuhaus, P., Siegismund, S., Schmidt, F. W., and Burdelski, M. Experiences with liver transplantation in Hannover. Hepatology 4:56S-60S, 1984.
14. Starzl, T. E. (with the assistance of Putnam, C. W.). *Experiences in Hepatic Transplantation.* W. B. Saunders, Philadelphia, 1969.

15. Starzl, T. E., Iwatsuki, S., Shaw, B. W., Jr., and Gordon, R. D. Orthotopic liver transplantation in 1984. Transplant. Proc. 17(1):250-258, 1985.
16. Starzl, T. E., Iwatsuki, S., Shaw, B. W., Jr., Nalesnik, M. A., Farhi, D. C., and Van Thiel, D. H. Treatment of fibrolamellar hepatoma with partial hepatectomy or with total hepatectomy and liver transplantation. Surg. Gynecol. Obstet. (In press, 1985).