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Long-term Results After Liver Transplantation for Primary Hepatic Epithelioid Hemangioendothelioma

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Background: Hepatic epithelioid hemangioendothelioma (PHEHE) is a multifocal, low-grade malignant neoplasia characterized by its epithelial-like appearance and vascular endothelial histogenesis. The outcome of 16 patients treated with orthotopic liver transplantation (OLT) is the subject of this report.

Methods: A retrospective study of 16 patients with HEHE (7 men, 9 women) with ages ranging from 24 to 58 years (mean 37 ± 10.6 years). Follow-up intervals ranged from 1 to 15 years (median of 4.5 years).

Results: Actual patient survival at 1, 3, and 5 years was 100, 87.5, and 71.3%, respectively. Disease-free survival at 1, 3, and 5 years was 81.3, 68.8, and 60.2%, respectively. The 90-day operative mortality was 0. Involvement of the hilar lymph nodes or vascular invasion did not affect survival. The 5-year survival of HEHE compares favorably with that of hepatocellular carcinoma at the same stage (stage 4A): 71.3 versus 9.8% ($p = 0.001$)

Conclusions: The long-term survival obtained in this series justifies OLT for these tumors even in the presence of limited extrahepatic disease.

Key Words: Liver transplantation—Epithelioid hemangioendothelioma.

Epithelioid hemangioendothelioma (EHE) is a low-grade malignant neoplasm derived from endothelial cells. It was first recognized in soft tissues (1), with later reports showing that the liver may also serve as a primary site (2). We have treated 16 cases of primary hepatic EHE with orthotopic liver transplantation (OLT), and they are the subject of this report.

MATERIALS AND METHODS

Patient profile

Between November 1976 and February 1993, 16 patients with the diagnosis of EHE were treated with OLT either at the University Health Sciences Center of Colorado (1976–1980) or at the University of Pittsburgh Medical Center (1981–1993). There were seven men and nine women, with ages ranging from 24 to 58 years (mean of 37 ± 10.6 years). Follow-up intervals ranged from 1 to 15 years (median of 4.5 years).

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Clinical features

The frequency of symptoms is depicted in Table 1. In five patients the tumor was found incidentally: in two patients during follow-up for previously treated cancer (squamous cell carcinoma of the nasopharynx and melanoma of the back), in one patient during evaluation of a back injury, in one patient during a laparotomy for endometriosis, and, finally, one patient discovered multiple lesions in her liver while performing an ultrasound examination on herself. Four of the nine women had taken oral contraceptives for indeterminate periods. No patient in this series had a history of exposure to hepatotoxins.

TABLE 1. *Clinical presentation*

Symptoms and signs	Frequency (%)	Mean duration (mos)
Abdominal pain	56.2	12.5
Weight loss	18.7	10
Fatigue	6.5	2
Anorexia	6.25	6
Jaundice	12.5	9.5
Ascites	6.25	12
Shoulder pain	6.25	1
Splenomegaly	6.25	24
Dyspnea	6.25	2
Cholangitis	6.25	1
Hepatomegaly	25	7
Incidental	31.25	8

Diagnosis

In 14 patients the diagnosis was confirmed before transplantation: in seven by percutaneous liver biopsy and in seven by open liver biopsy. In the remaining two patients the diagnosis was obtained at the time of the transplant.

Four patients had been misdiagnosed originally. In three cases, 1–5 years before transplant, the liver biopsies were interpreted as hemangiomas (and one of these patients had a separate biopsy interpreted as a sarcoma). One patient had a nondiagnostic percutaneous biopsy. In one case the native liver also had unsuspected cirrhosis (the only case of cirrhosis associated with EHE in this series).

The extent of the tumor was staged according to the pTNM classification (3,4). Fourteen patients were stage IV-A and two were stage IV-B.

Treatment

All patients underwent a standard orthotopic liver transplantation (5). The first patient in our series also had a concomitant excision of a pulmonary nodule. Five patients received chemotherapy with Adriamycin-based regimens: one preoperative, three postoperative, and in one case before and after the transplant. An additional three patients had radiotherapy, two preoperatively and one after surgery. Baseline immunosuppression was accomplished with azathioprine and prednisone in one patient, with cyclosporine and prednisone in 10 patients and with FK506 and prednisone in the remaining five patients.

Statistical analysis

Survival analysis was performed using the method of Kaplan-Meier. Differences between groups were tested for significance using Breslow's test, with the significance level set at 0.05.

RESULTS

Actuarial patient survival at 1, 3, and 5 years was 100, 85.7, and 71.3%, respectively (Fig. 1). Nine of 16 patients (65%) are alive and free of tumor; seven of these patients have had follow-up intervals >5 years (median of 7.5 years). Diffuse metastatic disease was responsible for death in five patients from 16 months to 180 months after OLT (median: 43 months). Two patients are alive with metastases: one with lung metastases 3 years after surgery, and the other with tumor in the liver 4 years after her transplant. This last patient was retransplanted but, unfortunately, there was residual tumor at the margins of the resection.

Disease-free survival at 1, 3, and 5 years was 81.3, 68.8, and 60.2%, respectively (Fig. 1). Involvement of the hilar lymph nodes or vascular invasion was a frequent feature, being present in nine patients (56.2%). Nevertheless, half of those patients are currently alive and free of disease. There was no difference in the recurrence rates among patients with positive or negative nodes (Fig. 2). Likewise, vascular invasion did not affect the recurrence rate (Fig. 3). The most common sites of recurrence were the liver, lung, and bone (Table 2).

There were six postoperative complications that occurred in five patients. One patient bled from the Roux-en-Y loop, requiring exploration on the 4th postoperative day. Eight months later he developed a biliary stricture that required percutaneous dilatation. Two patients needed a second graft because of primary nonfunction, at 2 and 4 days after transplant, respectively. One patient required thrombectomy on the 4th postoperative day due to hepatic artery thrombosis. Finally, one patient received a second graft (for liver recurrence, 4 years

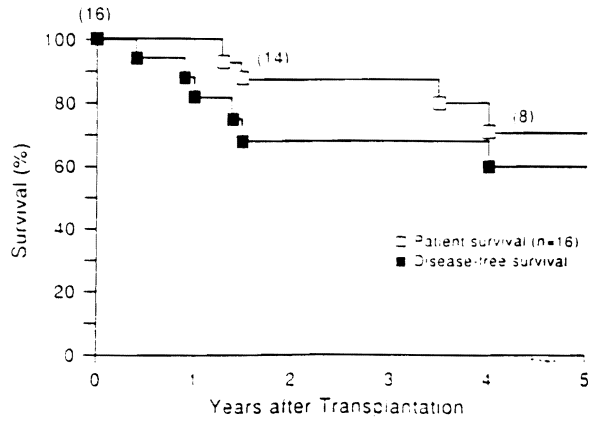

FIG. 1. Actuarial and disease-free survival.

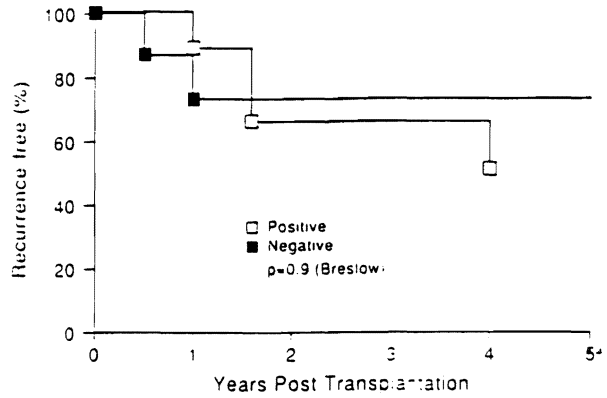

FIG. 2. Hilar lymph node status and recurrence after transplantation.

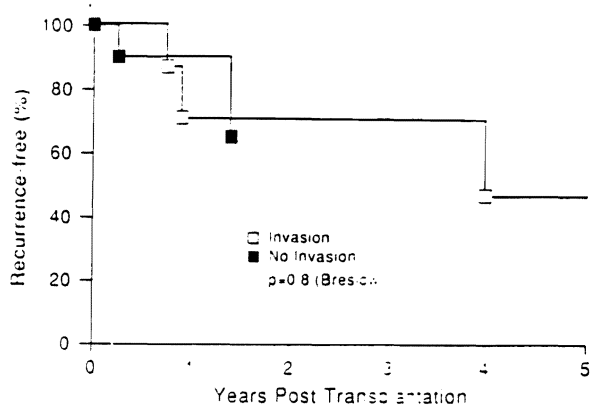

FIG. 3. Vascular invasion and recurrence after transplantation.

after the primary transplant), and developed a biliary leak and intraabdominal abscess. 10 and 14 days after her retransplant, respectively. She was finally discharged, after a prolonged hospital course. All patients recovered from their complications.

DISCUSSION

EHE is a soft-tissue malignant tumor that is characterized by its epithelial-like appearance and vascular endothelial histogenesis. It was histologically identified by Weiss and Enzinger in 1982 (1), and in 1984 Ishak et al. first reported a series of 32 primary EHE of the liver (2). In 1988, we reported the first series of patients (10 cases) (6) with unresectable hepatic epithelioid hemangioendothelioma (HEHE) that were treated with liver transplantation. This report updates that initial series, and adds an additional six cases that we have treated since.

Liver transplantation for hepatic malignancy remains surrounded by controversy, stemming from the fact that hepatocellular carcinomas and cholangiocarcinomas are associated with a high recurrence rate after liver transplantation (7,8).

The clinical presentation of HEHE is usually nonspecific. The true incidence of this tumor is not yet known, and it is possible that many of these tumors have been misdiagnosed, especially before Ishak's report in 1984 (9). The only risk factors known in these patients were the use of oral contraceptives (10). Often, a wedge biopsy of the tumor is necessary to recognize the architectural features such as the intravascular or intrasinusoidal growth pattern characteristic of the neoplasm (2,6,11). Immunohistological staining for Von Willebrand factor

TABLE 2. *Recurrence and survival*

Case no.	Primary	Age/sex	Recurrence	Site of recurrence	Time to recurrence (yrs)[a]	Survival time (yrs)[a]	Outcome
1	HEHE	28/F	Yes	Liver	14	15	DWT
2	HEHE	50/M	Yes	Liver lung	3.4/1.5	3.5	DWT
3	HEHE	43/M	Yes	Lung	0.9	3	AWT
4	HEHE	53/M	Yes	Bone lung	0.3/0.9	1.4	DWT
5	HEHE	38/M	Yes	Liver lung	2.8/1.4	4	DWT
6	HEHE	28/M	No	NA	NA	7.8	AWOT
7	HEHE	28/M	No	NA	NA	3.7	AWOT
8	HEHE	41/F	No	NA	NA	6.3	AWOT
9	HEHE	31/F	No	NA	NA	3.7	AWOT
10	HEHE	46/F	Yes	Liver	4	5	AWT
11	HEHE	25/F	Yes	Liver lung	1.1	1.3	DWT
12	HEHE	29/F	No	NA	NA	6	AWOT
13	HEHE	58/M	No	NA	NA	1.8	AWOT
14	HEHE	33/F	No	NA	NA	10.5	AWOT
15	HEHE	24/F	No	NA	NA	7.3	AWOT
16	HEHE	32/F	No	NA	NA	7.2	AWOT

HEHE, hepatic epithelioid hemangioendothelioma; AWOT, alive without tumor; AWT, alive with tumor; DWT, died with tumor.
[a] From day of transplant.

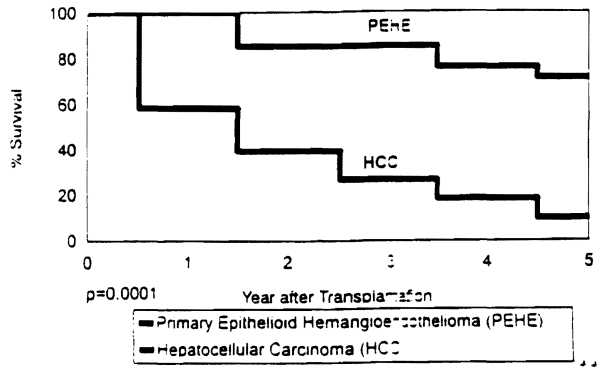

FIG. 4. Survival after liver transplantation for stage IV-A hepatic hemangioendothelioma (n = 14) versus hepatocellular carcinoma (n = 102).

may also be of use in distinguishing the endothelial-derived tumor cells from adenocarcinoma (2). Because of the variable cellularity within any given tumor nodule, needle biopsy may be nondiagnostic if only a fibrous tissue area is sampled. Relying on only the cytologic appearance may result in overgrading the lesion as a highly malignant angiosarcoma, rather than a low-grade malignancy. This, obviously, could result in limiting the treatment plan to conservative medical management, excluding the possibility of a liver transplant. In point of fact, 4 of 16 patients in the current series had an initial incorrect diagnosis.

A direct comparison between the report of Ishak et al. (2) of 32 patients with HEHE and the current series of 16 patients treated with liver transplantation is not possible. However, it is interesting to note that only 9 of 32 (28%) of the Ishak et al. patients without any specific therapy survived >5 years. The actuarial survival rate of the HEHE patients treated with liver transplantation in the current series (71.3% at 5 years) is quite similar to that which we see in patients transplanted for nonmalignant disease (12). The survival after OLT for stage IV-A HEHE (n = 14) compares more than favorably with that of hepatocellular carcinoma at the same stage (unpublished data, Fig. 4).

Obviously, it remains difficult to propose a single standard therapeutic approach for these tumors because of their rarity and unpredictable natural history. According to Weiss and Enzinger (1), the histologic features of HEHE do not predict tumor behavior, and consequently it is not possible to use the histologic characteristic of a given liver EHE as a guide for therapeutic decisions. Hepatic EHE is usually multifocal (1,2,6,11) and, therefore, not suitable for partial hepatectomy (6,13–16). The role of chemotherapy without liver transplantation is unknown because only a few cases have been published in the literature (15,17); however, in our own series there was no response (data not shown). Thus, total hepatectomy and OLT is the surgical therapeutic procedure of choice. The long-term survival and disease-free survival after liver transplantation reported in this article confirms the unique nature of this malignant tumor. Even after the development of metastases, three patients survived for >2 years. It is also interesting that in the subset of nine patients with vascular invasion and positive hilar lymph nodes at transplant (findings that usually condemn to a rapid death from recurrence in all the other primary liver tumors), there were no mortalities and all of them are free of disease. Seven patients had recurrence, and five of them died as a result. The survivals were similar in patients with positive and negative nodes. We do not have sufficient data to define a role for chemotherapy, radiotherapy, or both in the treatment of this neoplasm. Thus, prospective studies will be required in this area.

In conclusion, liver transplantation appears to be a very reasonable therapeutic approach for hepatic EHE when the tumor is not resectable (other than with a total hepatectomy). The long-term survival obtained in this series justifies liver transplantation for these tumors, even in the presence of limited extrahepatic disease.

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