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# Clinicopathologic Factors Affecting Patient Survival and Tumor Recurrence After Orthotopic Liver Transplantation for Hepatocellular Carcinoma

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THE role and value of orthotopic liver transplantation (OLTx) in the treatment of primary hepatic malignancies have been debated because of high tumor recurrence rates.[1-4] Certain clinicopathologic entities have been shown to influence patient survival rates for hepatocellular carcinoma (HCC).[3,4] In the current study, we analyzed various histopathologic features in the livers of 106 liver transplant recipients with HCC for their influence on patient outcome.

## PATIENTS METHODS

During the period from January 1980 to December 1989, 106 (6%) of a total of 1,786 patients underwent OLTx because of the presence of HCC. They received cyclosporine-steroid combination therapy for their basic immunosuppression. Chemotherapy was given to many of the patients during the postoperative period, but the treatment was not based on a uniform protocol.

The influence of the following risk factors was assessed: (1) tumor size, (2) tumor number, (3) shape of the tumor (circumscribed or infiltrative), (4) tumor distribution within the liver (uni- or bilobar), (5) pseudocapsular formation, (6) vascular invasion, (7) liver capsule invasion, (8) tumor involvement at the resection margin, (9) lymph node metastasis, (10) hepatitis B, (11) cirrhosis, and (12) fibrolamellar variant.

The diagnosis of tumor recurrence was made using various radiologic imaging techniques, persistent elevation of serum alpha-fetoprotein, exploratory surgery, or autopsy. The median follow-up period was 30 months, with a range of 12 to 124 months.

Data are shown as mean ± SE. For patient survival and disease-free period, data analysis was performed by the method of Kaplan-Meier. A $P$ value of less than 0.05 was considered to be significant.

## RESULTS

The mean age of the 106 patients was 43.4 ± 1.8 years (range: 2 to 70 years). There were 71 males and 35 females. Sixty-five patients (61.3%) eventually died during the follow-up period, 17 within 3 months of OLTx. The timing and cause of the deaths are summarized in Table 1. While noncancerous complications were responsible for all deaths within 3 months of OLTx except for that of 1 patient, tumor recurrence was considered to be a direct cause of death in 36 of the 48 patients who survived more than 3 months after OLTx. In patients who died of causes other than their tumors, 4 were found to have recurrence of their tumor, which did not directly contribute to their death.

In addition, 5 patients were alive with tumor recurrence at the time of last follow-up. Therefore, tumors recurred in a total of 45 patients or 51% of the patients who survived more than 3 months. Eighty-five percent of the recurrences occurred within 12 months of OLTx.

**Table 1. Timing and Cause of Death in 65 Patients Who Died After OLTx for HCC**

| Cause | Posttransplant <3 mo | Posttransplant ≥3 mo |
|---|---|---|
| Intraoperative death | 2 | |
| Liver failure due to technical reason | 3 | |
| Liver failure other than technical reason | 5 | |
| Systemic sepsis | 6* | 2 |
| Lymphoproliferative disorders | 1 | 1 |
| Recurrent hepatitis | | 6† |
| Rejection | | 1 |
| Myocardial infarction | | 1* |
| AIDS | | 1 |
| Cancer | | 36 |
| Total | 17 | 48 |

*Including 1 patient with coincident recurrent cancer.
†Including 2 patients with coincident recurrent cancer.

The survival rates of the 106 patients with HCC were 65%, 39%, and 38% at 1, 3, and 5 years, respectively, after OLTx. On the other hand, the survival rates of 1,622 patients who underwent OLTx for nonmalignant liver diseases were 73%, 69%, and 67% at 1, 3, and 5 years, respectively, after OLTx. The survival rates of the former were significantly lower than those of the latter ($P < .001$) (Fig 1).

The tumors of 11 of 106 patients (10.4%) had fibrolamellar variant HCC (FL-HCC). The overall disease-free period of patients with FL-HCC was similar to that of patients with non-FL-HCC. However, in the patients with tumors of 5 cm or greater, the disease-free period of patients with FL-HCC was significantly longer than that of patients with non-FL-HCC ($P < .05$) (Fig 2). The influence of each factor on the incidence of tumor recurrence in 9 patients with FL-HCC who survived 3 months is examined in Table 2.

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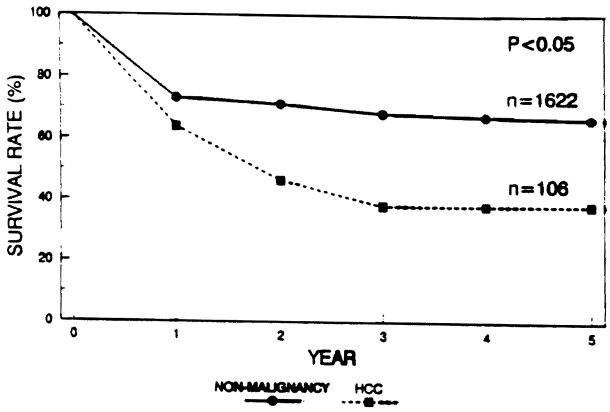


**Fig 1.** Patient survival rates after OLTx for HCC (n = 106) and for nonmalignancy (n = 1,622) ($P < .05$).

The influence of the above mentioned 12 clinicopathologic factors on the disease-free period was studied in the patients with non-FL-HCC (Table 3, univariate analysis). Sixteen patients with non-FL-HCC who died without recurrence within 3 months postoperatively were excluded, leaving 80 patients for the analysis. The favorable factors for disease-free period were tumor size of less than 5 cm in diameter, single tumor, no vascular invasion, no lymph node metastasis, presence of pseudocapsule, circumscribed tumor, absence of margin invasion, and unilobar involvement. Among all of the factors, absence of vascular invasion was associated with the lowest rate of recurrence ($P < .0001$).

Multivariate analysis of these factors revealed that tumors with gross vascular invasion were associated with an incidence of recurrence 42 times higher than that of tumors without such invasion. Other factors that independently affected tumor recurrence in order of decreasing frequency

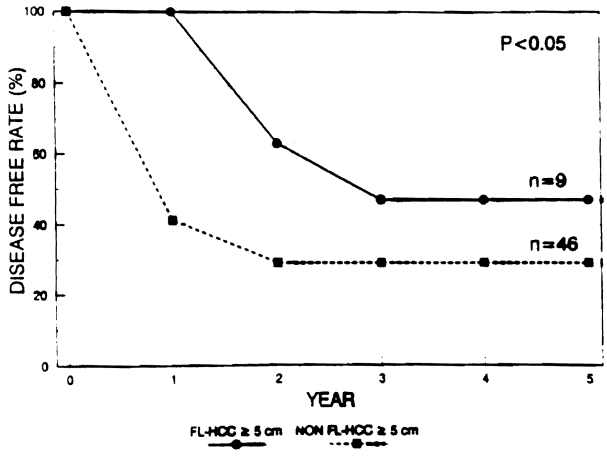


**Fig 2.** Disease-free survival rates for patients with FL-HCC (n = 9) and patients with non-FL-HCC (n = 46) who survived more than 3 months after receiving their transplant. Tumors less than 5 cm in diameter were excluded ($P < .05$).

**Table 2. Incidence of Recurrence Within 3 Years After Liver Tx in 9 Patients with FL-HCC (3-Month Survivors)**

| Tumor Character | No.* | No. Patients with Recurrence |
|---|---|---|
| Tumor size | | |
| <5 cm | 1 | 0 |
| ≥5 cm | 8 | 4 |
| Tumor number | | |
| Single | 2 | 0 |
| Multiple | 7 | 4 |
| Vascular invasion | | |
| (−) | 3 | 0 |
| Microscopic | 1 | 1 |
| Macroscopic | 5 | 3 |
| Pseudocapsule | | |
| (−) | 8 | 3 |
| (+) | 0 | 0 |
| Lymph node | | |
| (−) | 7 | 3 |
| (+) | 2 | 1 |
| Tumor shape | | |
| Circumscribed | 6 | 2 |
| Infiltrative | 2 | 1 |
| Capsular invasion | | |
| (−) | 8 | 4 |
| (+) | 1 | 0 |
| Margin | | |
| (−) | 9 | 4 |
| (+) | 0 | 0 |
| Hepatitis B | | |
| (−) | 9 | 4 |
| (+) | 0 | 0 |
| Cirrhosis | | |
| (−) | 8 | 4 |
| (+) | 1 | 0 |
| Involvement of lobes | | |
| Unilobe | 1 | 0 |
| Bilobe | 8 | 4 |

*Data not available for some patients.

were microvascular invasion, non-FL-HCC, bilobar distribution, and absence of pseudocapsular formation (Table 4).

When the tumors were classified by their TNM stage, the survival rates of patients with tumors in stages I (n = 3) and II (n = 19) were significantly better than those of patients with tumors in stages III (n = 23) and IV (n = 50) (Fig 3).

## DISCUSSION

Tumor recurrence is a major cause of patient death after OLTx for HCC. In the present study, the rate of recurrence was found to be well correlated with certain distinctive pathologic features.

In this analysis, the most statistically significant adverse prognostic factor was macroscopic vascular invasion by tumor. Other adverse prognostic factors of significance included tumor size 5 cm in diameter or greater, multifocality of the tumor, infiltrating type (in contrast to nodular,

**Table 3. Clinicopathologic Factors and Disease-Free Period in Patients with Non-FL-HCC (3-Month Survivors)**

| Factor | No. | Disease-Free (%) 1 y | 3 y | 5 y | P Value |
|---|---|---|---|---|---|
| Tumor size | | | | | |
| <5 cm | 34 | 75.4 | 71.4 | 71.4 | $P < .001$ |
| ≥5 cm | 46 | 41.3 | 29.1 | 29.1 | |
| Tumor number | | | | | |
| Single | 23 | 82.6 | 78.0 | 78.0 | $P < .005$ |
| Multiple | 57 | 46.0 | 33.3 | 33.3 | |
| Vascular invasion | | | | | |
| (−) | 22 | 95.2 | 95.2 | 95.2 | $P < .0001$ |
| Microscopic | 30 | 70.0 | 49.8 | 49.8 | |
| Macroscopic | 28 | 11.9 | 0.0 | | |
| Pseudocapsule | | | | | |
| (−) | 63 | 51.1 | 37.0 | 37.0 | $P < .01$ |
| (+) | 17 | 81.6 | 81.6 | 81.6 | |
| Lymph node | | | | | |
| (−) | 76 | 59.8 | 49.2 | 49.2 | $P = .09$ |
| (+) | 4 | 0.0 | | | |
| Tumor shape | | | | | |
| Circumscribed | 55* | 70.0 | 63.2 | 63.2 | $P < .001$ |
| Infiltrative | 24 | 25.1 | 0.0 | | |
| Capsular invasion | | | | | |
| (−) | 72 | 57.5 | 47.2 | 47.2 | $P = .1$ |
| (+) | 8 | 43.8 | 43.8 | 43.8 | |
| Margin | | | | | |
| (−) | 74 | 74.3 | 55.9 | 52.2 | $P < .05$ |
| (+) | 6 | 33.3 | 0.0 | | |
| Hepatitis B | | | | | |
| (−) | 60 | 60.6 | 50.4 | 50.4 | $P = .3$ |
| (+) | 20 | 42.7 | 36.6 | 36.6 | |
| Cirrhosis | | | | | |
| (−) | 59 | 59.3 | 52.2 | 52.2 | $P = .2$ |
| (+) | 21 | 48.0 | 33.6 | 33.6 | |
| Involvement of lobes | | | | | |
| Unilobe | 44 | 81.6 | 67.6 | 67.6 | $P < .0001$ |
| Bilobe | 36 | 28.5 | 28.5 | 28.5 | |

*Data not available for 1 patient.

circumscribed type) of tumor, and bilobar involvement. Although the frequency of lymph node involvement by tumor or positive resection margin is relatively small (less than 5%), patients with these adverse factors were invariably found to have early tumor recurrence.

**Table 4. Relative Risk of Tumor Recurrence by Multivariate Analysis**

| Factor | Relative Risk |
|---|---|
| Gross vascular invasion | 42 |
| Microscopic vascular invasion | 18 |
| Non-FL-HCC | 16 |
| Bilobar distribution | 6 |
| Pseudocapsular formation | 4 |

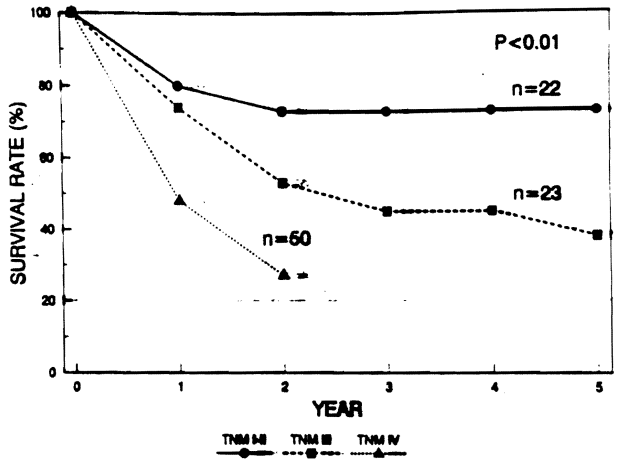


**Fig 3.** Comparison of patient survival rates among TNM stage I and II (n = 22), III (n = 23), and IV (n = 50) tumors for patients with non-FL-HCC. The differences were significant among the groups ($P < .01$).

Factors that were significantly associated with a better prognosis included tumor size less than 5 cm in diameter and pseudocapsular formation. Fibrolamellar variant was also a favorable factor that independently affected the prognosis. This subtype tumor of HCC, which often presents in transplant candidates when the disease is at an advanced stage, is characterized by its less invasive and slow-growing nature.[5]

Survival of patients with non-FL-HCC was inversely related to TNM stage. The survival of patients with stage I and II tumors far exceeded that of other groups (stages III and IV). A similar observation was reported by the Hanover group.[3] There were no long-term survivors seen in patients with stage IV tumors. For this poor prognostic group, adjuvant anticancer therapy may prolong the tumor-free survival rate. Recently, we started to investigate systemically the value of adjuvant therapy before and after transplantation for patients with hepatic malignancy.

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