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Accelerated Growth Rates of Recurrent Hepatocellular Carcinoma After Liver Transplantation

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Abstract

The growth rates of recurrent hepatocellular carcinoma (HCC) after orthotopic liver transplantation (OLTX) were estimated by calculating the tumor doubling time (TDT) in 20 patients. The mean TDT, calculated by multiple measurement of tumor size, was 44.3 ± 11.3 days (mean ± standard error) in 12 patients with pulmonary metastasis (range, 10 to 161 days) and 37.6 ± 8.9 days (range, 7 to 65 days) in 5 patients with liver allograft recurrence. The TDT as estimated by serum alpha-fetoprotein (AFP) levels in 6 patients was 37.3 ± 10.0 days (range, 12 to 84 days). The mean TDT obtained from 5 control subjects with HCC who were treated with liver resection (without immunosuppression) was 273.8 ± 79.1 days (range, 82 to 560 days). The disease-free period and survival time after OLTX both correlated well with the TDT (r = 0.546 and r = 0.701, respectively). The patients with fibrolamellar HCC had a greater TDT and a longer survival time than those with nonfibrolamellar HCC. Despite a wide range of TDT in patients who received transplants, their recurrent HCC tumors grew significantly faster than those of patients with the same disease who did not receive transplants. The factors involved in this accelerated growth rate may include the use of immunosuppressive drugs and the consequent suppression of host immunity against the growth of micrometastasis.

Patient survival after orthotopic liver transplantation (OLTX) for primary hepatic malignant disease is hampered by tumor recurrence. Also, survival time is significantly lower than that for nonmalignant liver diseases.[1–6] It bas been speculated that immunosuppressive therapy accelerates tumor growth,[1,7–8] but this has not been documented in clinical transplantation.

In this study, we examined the growth rates of recurrent hepatocellular carcinomas (HCC) after OLTX during immunosuppressive therapy by calculating tumor doubling time (TDT). The growth rates during immunosuppression were compared with those after hepatic resection without immunosuppression and to those reported in the literature.

Patients and Methods

Between January 1980 and July 1989, 100 patients with HCC underwent OLTX at the University Health Sciences Center of Colorado (1980) and the University Health Center of Pittsburgh (since 1981).

All patients received cyclosporine and steroid combination therapy as basic immunosuppression. Some patients received adjuvant chemotherapy that primarily consisted of doxorubicin (Adriamycin, Adria Laboratories, Columbus, OR) in varying doses and

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schedules, without a uniform protocol. Once recurrent disease was diagnosed, most patients received some form of chemotherapy.

Tumor recurrence, was documented in 43 of 100 patients (43%) during the median follow-up time of 34 months (range, 12 to 124 months). The size of the recurrent tumor could be measured in 27 lesions (15 in the liver allograft and 12 in the lung) of 20 patients. In 17 of the 27 lesions (12 in the lung and 5 in the liver), the size of the tumor could be measured on multiple occasions.

The size of the recurrent tumor in the liver allograft was measured by computed tomography (consecutive sections were ≤ 1.0-cm thick) in 13 patients (at autopsy in 1 patient and at surgery in 1 patient). The size of the metastatic lesions in the lung was measured by a chest radiograph.

Five patients who underwent liver resection only for HCC and whose tumors were resected were used as control subjects for comparison of TDT with the patients who underwent transplantation and immunosuppression.

All of the recurrent tumors were 5 cm or less in greatest diameter at the time of diagnosis of the recurrence.

The TDT was calculated by the following formula developed by Schwartz:[9]

$$\text{TDT (tumor doubling time)} = \frac{t \log (2)}{3 \log (D_2/D_1)}$$

where D (D_1 or D_2) is a mean value of the largest diameter and a diameter perpendicular to it, in millimeters. D_1 is the tumor diameter at the first measurement, D_2 is the tumor diameter at the second measurement, and t is the time interval (days) between the measurements (two-point measurement). When the TDT were obtained on multiple occasions, the average value of the growth rates was used.

In ten patients for whom only a single time point measurement was available, the TDT was calculated based on the assumption that the size of the microdeposits of the original HCC was 1 mm in diameter ($D_1 = 1$; one-point measurement). Based on this assumption, TDT was calculated when D_1 was given an arbitrary value of 1 in the above formula.

Serum alpha-fetoprotein (AFP) levels have been used for estimations of TDT in other studies.[10] Therefore, in this study we correlated changes in AFP levels with objective tumor measurement in some of the patients to compare the values obtained by these two methods.

Linear regression analysis was used to evaluate the relationship between TDT and survival time or the disease-free period. The chi-square analysis and Student's *t* test were used to compare the differences between the groups. The difference was considered significant when the *P* value was less than 0.05.

Results

The TDT and other clinical information for 20 patients who underwent OLTX is summarized in Table 1. The TDT was obtained by two-point measurement in 5 of patients who had tumor recurrence in the liver allograft. The mean TDT was 33.0 ± 7.1 days. One patient with fibrolamellar HCC had the longest TDT of 51 days. The mean TDT for nonfibrolamellar HCC was 29.5 ± 7.4 days (four patients) (Table 1). These values were

compared with those of 5 control subjects with recurrent HCC after liver resection (with no immunosuppression), in whom the mean TDT was 273.8 ± 79.1 days (Table 2). One patient with fibrolamellar HCC had the longest TDT of 560 days after liver resection. The mean TDT for nonfibrolamellar HCC in this group was 202.3 ± 58.1 days (four patients), which was significantly longer than that for recurrent tumor after OLTX ($P < 0.001$).

The mean TDT for the pulmonary metastases in 12 patients was 44.3 ± 12.1 days. Two patients with fibrolamellar HCC had the longest TDT (161 and 73 days), and the mean TDT for nonfibrolamellar HCC was 29.8 ± 5.3 days (ten patients) (Table 1). No difference was noted between the TDT of liver allograft and pulmonary recurrences in patients with nonfibrolamellar HCC.

The mean TDT obtained from serum AFP levels in 6 patients with nonfibrolamellar HCC was 37.3 ± 10.0 days (Table 1). This value was not significantly different from the TDT calculated by the tumor sizes of the liver allograft recurrences or pulmonary metastases.

The TDT obtained by one-point measurement in 15 patients with allograft recurrence was 18.0 ± 3.1 days (Table 1), which was shorter than that obtained by two-point measurement. However, when a comparison was made with four patients with nonfibrolamellar HCC who were available for two-point measurement, the mean TDT by one-point measurement was 22.5 ± 4.0 days, which was not significantly different from that obtained by two-point measurement.

The change in tumor diameter during the time after OLTX in 12 patients with pulmonary metastasis is shown in Figure 1. One patient had temporary regression of the tumor and another patient had tumor growth retardation after initiation of aggressive chemotherapy. In three other patients, however, the tumor growth rate was relatively constant at each time point measured despite chemotherapy. One of the patients with the shortest TDT (10 day) did not receive any anti-cancer treatment.

Tumor growth curves were similar for 15 patients with allograft recurrence (Fig. 2). For those whose tumor size was measured twice, tumor growth rates between two sets of different time points were similar. The shortest TDT (4 days) was seen in a patient with positive hepatitis-B surface antigen and cirrhosis (Fig. 2 and Table 1).

Tumor growth curves were also obtained for five patients who underwent liver resection (Fig. 3). Their clinical information and TDT are shown in Table 2.

The survival time of the 20 patients ranged from 4.6 to 83.0 months (mean, 18.2 ± 3.7 months). Their disease-free period ranged from 0 to 20.7 months (mean, 7.6 ± 1.1 months). Of two patients with fibrolamellar HCC, one had the longest survival time and the other had the longest disease-free period (Table 1). The survival time, and disease-free period were plotted against TDT (Fig. 4). The shorter the TDT, the shorter the survival time and disease-free period ($P < 0.0001$ and $P < 0.0001$, respectively). Tumor recurrence was noted within 12 months after OLTX in all but one of the patients with nonfibrolamellar HCC with TDT of less than 50 days (majority). All but one of these patients died within 24 months (Fig. 4).

Discussion

Tumor growth rate can be a useful predictor of survival because it is an indicator of the biologic nature of the tumor. Clinically, the tumor growth rate has been found to be inversely proportional to both the length of the disease-free period and the survival rate.[11–12]

The literature on TDT in HCC has been minimal. Using ultrasonography, Sheu *et al.* obtained TDT of 29 to 398 days (mean, 136 days) for 28 patients with small HCC (≤ 5 cm in diameter), most of whom had cirrhotic livers.[13] The TDT for the two noncirrhotic livers were 44 and 76 days. In a similar study reported by Ebara *et al.*,[14] the TDT for 21 patients with small HCC (≤ 3 cm in diameter) in cirrhotic livers was 30 to 540 days (mean, 195 days). Okazaki *et al.* found that the average TDT for 15 patients with HCC (in 10 cirrhotic and 5 noncirrhotic livers) was 102 days (range, 41 to 305 days).[15] The average TDT for the five noncirrhotic livers in this study was 132 days (range, 39 to 226 days). These findings provide further support for the belief that many HCC are slow-growing tumors.

Johnson and Williams studied 40 patients with HCC who underwent various treatments (including liver transplantation) and showed that the TDT calculated by serum AFP level could be used for estimation of tumor progression.[10] They reported that the TDT ranged from 6.5 to 112 days (mean, 41 days) for all of the patients. In two of six patients who underwent OLTX, recurrence was suspected when the AFP level rose. In this study, TDT for the patients who underwent immunosuppression were not compared with those for the patients who did not undergo immunosuppression. However, the slope of the accompanying figures plotting time against AFP level illustrated that TDT was markedly shortened compared with the other group of patients. AFP level would be expected to correlate with viable tumor mass rather than tumor size.14 In fact, serum AFP level usually does not reflect the size of the tumor in humans,15–16 in contrast to animal studies.17 In the current study, however, TDT for AFP level were comparable with those obtained for tumor volume.

In the current study, the TDT for HCC after liver transplantation (under immunosuppression) was less than 50 days in most of the cases when one-point or two-point measurement was used. Notable exceptions were patients with fibrolamellar HCC. We found that the growth rate of the recurrent tumors in patients receiving immunosuppression is significantly greater than that of those who are not receiving immunosuppression. This indicates that immunosuppression may play a major role in the progression of tumor recurrence in the complex post-OLTX settings.

Because it is unlikely that tumors develop *de novo* in the liver allograft within 1 or 2 years after liver transplantation, recurrent HCC is likely the result of either metastasis from undiagnosed distant metastases that had been present before OLTX, or spillage of cancer cells at the time of surgical manipulation.[4] Therefore, recurrent HCC in the liver allograft must be secondary to the arrest of a cluster of cancer cells in the blood vessels that have escaped from the original tumors. The estimated tumor diameter of 1 mm may be an over-calculation because the diameter of the microvessels is much smaller. Moreover, if the size of the initial metastatic implant was less than 1 mm in diameter, the TDT of the recurrent HCC in the liver allograft would become even shorter.

Immunosuppression has been thought to accelerate residual tumor growth in humans after liver transplantation.[10] Animal studies have shown that in many tumor systems that can be transplanted, depression of host immunity increases the incidence of tumor metastasis.[18–20] Natural host defense mechanisms against tumor cells mediated by natural killer cells are believed to become impaired by immunosuppressive drugs that depress cell-mediated immunity.[21]

Cytokines, bacterial endotoxin, or coagulation factors (humoral factors that are released during the perioperative period of liver transplantation) may also play a role in tumor progression.[22–23] They alter endothelial surface properties, enhancing metastasis formation, 24 or directly damage the liver parenchyma, which may increase the metastatic potential of the liver.25–[26]

Despite the complexity of the mechanisms in tumor metastasis after liver transplantation, the current study demonstrates that the growth rate of recurrent HCC is markedly increased in the patient who receives a liver transplant along with immunosuppression. Further understanding of metastatic tumor biology and sophisticated use of immunosuppressive agents may contribute to prolonging patient survival after liver transplantation for HCC.

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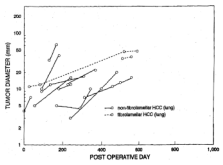

FIG. 1.

The diameter of the metastatic tumors is plotted on the logarithmic scale in relation to the time after OLTX for HCC in 12 patients with pulmonary metastasis (including 2 patients with fibrolamellar HCC).

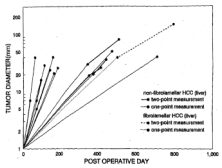

FIG. 2.

The diameter of the recurrent HCC in liver allografts is plotted in relation to the time after OLTX in 15 patients, including 1 patient with fibrolamellar HCC. In five patients, tumor size was measured twice and the resulting tumor growth curves are shown. Tumor growth curves were generated by both two-point and one-point measurements.

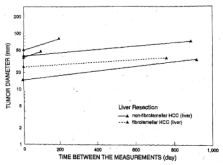

FIG. 3.

The diameter of the tumor (three patients with nonfibrolamellar HCC and one patient with fibrolamellar HCC without immunosuppression therapy) and tumor growth curves in relation to time are shown.

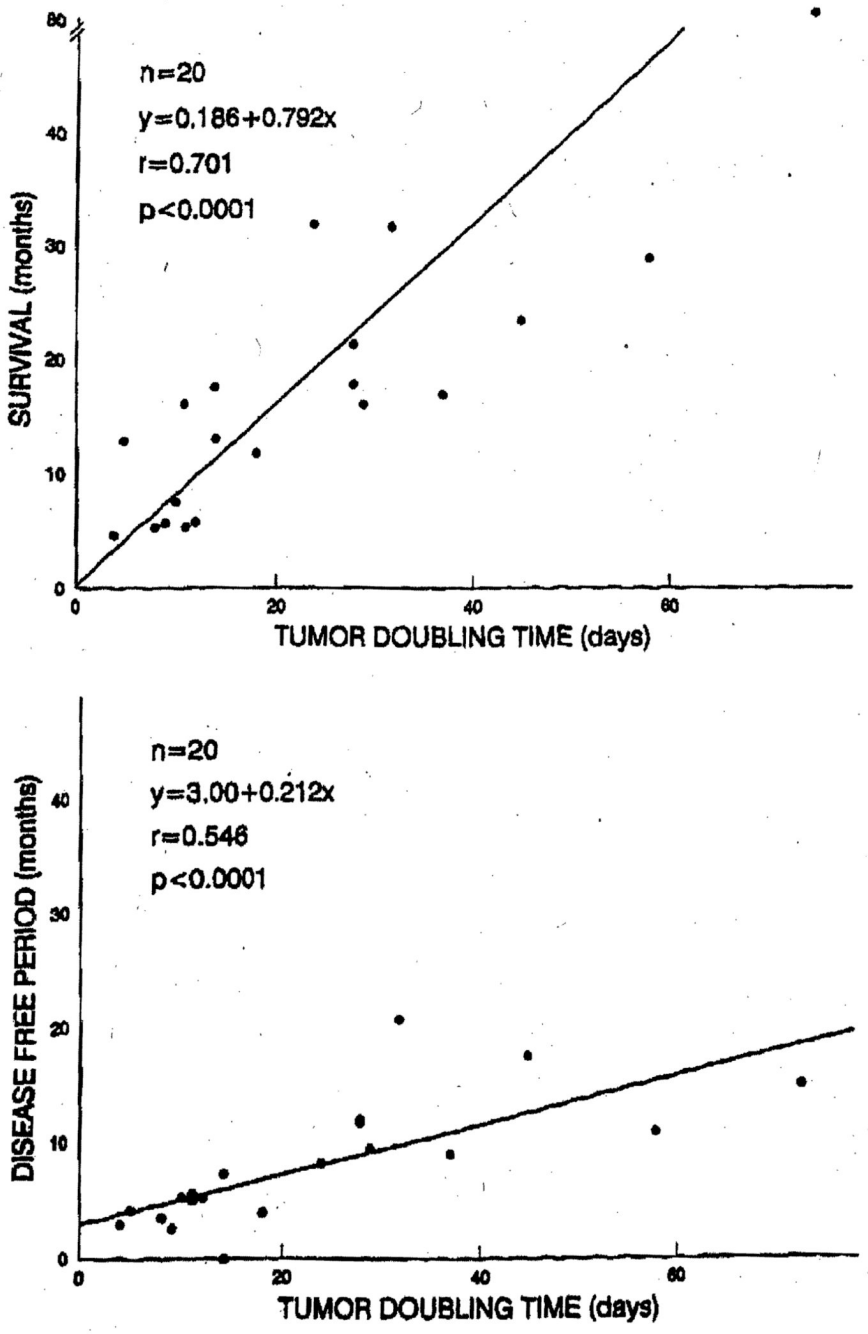

FIG. 4.

(Top) Survival times of 20 patients with HCC are plotted in relation to TDT with significant correlation. (Bottom) A significant correlation is also seen between the DFP and the TDT in the same group of patients.

TABLE 1

Tumor Doubling Time in 20 Patients With Liver Transplantation

				Tumor doubling tumor (days)					
				Liver					
Case no.	CIR	HB	FL-HCC	Two-point measurement	One-point measurement	Lung	AFP level†	PST (mo)	DFP(mo)
(OLT no.)									
231	−	−	+			73		83.0	12.9
324	−	−	−		11	46		16.1	5.0
338	−	−	+	51	32	161		31.7	20.7
344	+	−	−		45			23.4	17.4
454	+	−	−	7	9		12	5.6	2.6
462	+	+	−			18		11.7	3.9
767	+	+	−			58		28.8	10.8
1012	−	−	−			37		16.9	9.0
1116*	+	−	−		8	10		5.3	3.5
1132	+	−	−		5	15		12.9	4.2
1280*	−	−	−	38	24		84	31.9	8.2
1466	+	+	−		4			4.6	2.9
1605	+	−	−		10			7.5	5.2
1659	−	−	−			14		17.6	0.0
1683	+	−	−	46	28	54	52	21.3	11.7
1684	+	−	−		14		27	13.0	7.3
1802	−	−	−		11			5.3	5.6
1838	−	−	−		28	27	17	17.8	12.0
1903	+	+	−	27	29	19	32	16.0	9.5
2076	+	−	−		12			5.7	5.2
Mean				33.0	18.0	44.3	37.3	18.2	7.6
SE (day)				7.1	3.0	11.3	10.3	3.7	1.1
No.				5	15	12	6	21	21

CIR: cirrhosis; HB: hepatitis-B surface antigen–positive; FL-HCC: fibrolamellar hepatocellular carcinoma; AFP: alpha-fetoprotein; PST: patient survival time; DFP: disease-free period; SE: standard error.

* No chemotherapy given during the observation period.

† The values estimated by the time required for the doubling of the AFP level.

TABLE 2

Tumor Doubling Time for Four Patients With Liver Resection

Case no.	CIR	HB	FL-HCC	Tumor doubling time (days) (two-point measurement)	PST	DFP
1	−	−	+	560	86.2	43.9
2	+	+	−	351	39.2	3.8
3	−	−	−	96	30.8	22.0
4*	−	−	−	82		
Mean (day)				272.5	52.1	23.2
SE				98.8	14.1	9.5
No.				4	3	3

CIR: cirrhosis; HB: hepatitis-B surface antigen–positive; FL-HCC: fibro-lamellar hepatocellular carcinoma; PST: patient survival; DFP: disease-free period; SE: standard error.

*Tumor size measured before liver resection.

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