Recurrence of Hepatocellular Carcinoma After Liver Transplantation: Patterns and Prognostic Factors Based on Clinical and Radiologic Features

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OBJECTIVE. The purpose of this study was to elucidate on the basis of clinicoradiologic features the patterns of and prognostic factors for recurrence of hepatocellular carcinoma after liver transplantation.

MATERIALS AND METHODS. Institutional review board approval and informed consent were waived for this retrospective study. The subjects were 119 patients (102 men, 17 women; mean age, 49.8 years) with unresectable hepatocellular carcinoma who underwent liver transplantation from September 1996 to May 2005 and survived more than 2 months. We evaluated the incidence, imaging features, cumulative disease-free survival rate, and prognosis for recurrence of hepatocellular carcinoma. We examined clinical, therapeutic, and pretransplantation contrast-enhanced CT findings as prognostic factors and analyzed them with multivariate analysis. The median follow-up period was 17.2 months (range, 2.0–102.4 months).

RESULTS. Recurrence was found in 16 (13.4%) of 119 patients and was most frequent in the liver, with no specific pattern. A multivariate stepwise Cox hazard model showed that the presence of portal venous thrombosis, more than 3-cm diameter of the largest tumor, and a viable tumor volume ratio greater than 10% were statistically independent prognostic factors. The 3- and 5-year cumulative disease-free survival rates for the entire cohort were 82.1% and 76.6%, respectively. Despite local therapy for a solitary metastatic lesion, recurrences were common. The mortality rate among patients with recurrent disease was 56.3%.

CONCLUSION. Recurrence of hepatocellular carcinoma after liver transplantation is common, and the prognosis is not favorable. The presence of portal venous thrombosis and tumor size greater than 3 cm on baseline CT are significant risk factors. Aggressive interventional therapy seems to be helpful as a bridge to liver transplantation.

Keywords: CT, hepatocellular carcinoma, liver, liver transplantation, recurrence

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Hepatocellular carcinoma with or without hepatic cirrhosis is one of the leading causes of death worldwide, especially in eastern Asia and some areas of Europe. The incidence is increasing steadily in western countries [1]. In patients with hepatocellular carcinoma and hepatic cirrhosis, liver transplantation has the dual advantages of managing the carcinoma and replacing cirrhotic liver. Therefore, liver transplantation is generally regarded as the ideal treatment, especially of patients with end-stage liver disease. Unfortunately, tumor recurrence is common [2].

Many investigators [3–18] have reported on the patterns of and prognostic factors for recurrence of hepatocellular carcinoma after liver transplantation. However, the prognostic factors investigated have been focused more on histopathologic and postoperative clinical data than on preoperative radiologic data. We believe that radiologic determination of the likelihood of recurrence of hepatocellular carcinoma after liver transplantation is as important as histopathologic and postoperative clinical determination. Radiologic studies are superior to other techniques in preoperative evaluation of the nature of the disease and prediction of clinical outcome.

The purposes of this study were, first, to elucidate the incidence, cumulative disease-free survival rate, and factors significant in prognosis of recurrence of hepatocellular carcinoma after liver transplantation exclusively on the basis of preoperative clinical and CT features and, second, to evaluate the patterns and prognosis among patients with recurrent tumors.

Materials and Methods

Patients

Because this clinical study was retrospective, the institutional review board of our hospital waived its approval and the need for informed consent from the

TABLE 1: Summary of Clinical Characteristics of Patients (*n* = 119) Treated with Liver Transplantation

Characteristic	Value
Sex (*n*)	
Men	102
Women	17
Parenchymal liver disease (*n*)	
Chronic hepatitis	4
Liver cirrhosis	115
Cause of liver disease (*n*)	
Hepatitis B virus	108
Hepatitis C virus	9
Alcohol	2
Child-Pugh class (*n*)	
A	16
B	32
C	71
Serum α-fetoprotein level at the time of liver transplantation (ng/mL)	1.0–130,655.0 (1,647.0)
History of treatment before liver transplantation (*n*)	
Absent	38
Present	81
Surgical resection	15
Transcatheter arterial chemoembolization	70
Radiofrequency ablation	26
Percutaneous ethanol injection therapy	2
Follow-up period (mo)	
Period of disease prevalence[a]	0.2–109.2 (4.6)
Period during which patients had untreated hepatocellular carcinoma	0–22.3 (2.7)
Type of liver transplantation (*n*)	
Living donor	93
Cadaveric	24
Living donor then cadaveric[b]	2

Note—Values in parentheses are means.
[a]From initial diagnosis of hepatocellular carcinoma to liver transplantation.
[b]Because of graft failure.

patients. A computerized review of the pathology database of our institution from September 1996 to May 2005 revealed a total of 150 patients who had hepatocellular carcinoma with or without liver cirrhosis in the total hepatectomy specimen obtained after liver transplantation. In all cases, the histopathologic finding was hepatocellular carcinoma. In most (96%, 144/150) of the patients, the preoperative diagnosis of hepatocellular carcinoma was based on the findings on contrast-enhanced multiphase CT. In the other six patients (size range of tumors, 0.3–1.1 cm) the diagnosis was made only at pathologic examination after liver transplantation, and the patients had no preoperative evidence of hepatocellular carcinoma. Because one of the purposes of our study was to evaluate the utility of CT in the prognosis of recurrence of hepatocellular carcinoma after liver transplantation, those six patients were excluded from our study population. Another 25 patients were excluded because of a short follow-up period (≤ 2 months) mainly as the result of perioperative mortality ($n = 16$). The remaining 119 patients (102 men, 17 women; mean age, 49.8 years; range, 27–68 years), who had a preoperative diagnosis of hepatocellular carcinoma based on radiologic findings with postoperative histopathologic confirmation and survived more than 2 months, were enrolled in the study. Tables 1 and 2 summarize the characteristics of these patients.

Imaging Examinations and Follow-up

CT examinations were performed with one of five helical scanners (HiSpeed CT/i, LightSpeed QX/i, LightSpeed Ultra, LightSpeed 16, GE Healthcare; Brilliance 40, Philips Medical Systems) with contrast enhancement. A total of 120 mL of nonionic contrast material (300 mg I/mL iopromide, Ultravist 300, Schering) was administered IV at a rate of 3 mL/s. In the initial period of this study, fixed imaging-delay times (30, 60–70, and 180 seconds after initiation of the injection of contrast medium) were used. The bolus-tracking technique was adopted when it became available. Using a single-detector helical CT scanner, we obtained images in a craniocaudal direction with a 7-mm slice thickness and a 7-mm interval. The parameters for the MDCT examination were 2.5- to 5.0-mm slice thickness and 2.5- to 5.0-mm intervals.

Follow-up CT was performed 1 month and then every 2–4 months after therapy for hepatocellular carcinoma in cases of radiofrequency ablation ($n = 26$) and percutaneous ethanol injection therapy ($n = 2$) and every 3–6 months in cases of transcatheter arterial chemoembolization ($n = 70$) and surgical resection ($n = 15$). In some cases in which liver transplantation was scheduled, interventional therapy was performed as a bridge to liver transplantation. After liver transplantation, the patients underwent regular follow-up evaluations with alternating liver sonography and liver CT every 4–8 months for detection of intrahepatic recurrences and with chest radiography every 2–4 months for detection of pulmonary metastasis. Image analysis was performed by consensus of two radiologists who used the methods of routine clinical practice.

TABLE 2: Summary of Tumor Characteristics in Patients (*n* = 119) with Hepatocellular Carcinoma Managed with Liver Transplantation

Characteristic	Value
Percentage with histologic confirmation	100
No. per patient	1–11 (2.7)
Single	49
Multiple	70
Size (mm)	
Overall[a]	5–150 (23.2)
Diameter of largest[a]	7–150 (29.0)
Sum of diameters[a]	10–220 (50.9)
Viable tumor volume ratio after interventional therapy (%)	0–100 (61.4)
0% (*n*)	17
10–90% (*n*)	56
100% (*n*)	46
Lobar distribution (*n*)	
Unilobar	85
Bilobar	34
Contact with hepatic capsule (*n*)	
Present	68
Absent	51
Tumor margin (*n*)	
Infiltrative margin present	11
Discrete in all tumor	108
Intrahepatic portal venous thrombosis (*n*)	
Present	14
Absent	105
Lymphadenopathy[b] (*n*)	
Present	30
Absent	89

Note—Values in parentheses are means.
[a]Tumor size measured on contrast-enhanced CT scans.
[b]More than 1 cm in shortest dimension in drainage pathway.

Diagnosis of Hepatocellular Carcinoma

Pathologic examination of the explanted liver was made by one hepatopathologist with 26 years of experience. The freshly explanted liver specimens were sliced serially from top to bottom at 5-mm intervals. Macroscopically visible treated or untreated neoplastic nodules were evaluated with microscopy after standard H and E staining. All of these analyses were conducted with methods used in routine clinical practice. In all cases, one radiologist conducted radiologic–pathologic correlation on the basis of

TABLE 3: Prognostic Factors for Recurrence of Hepatocellular Carcinoma After Liver Transplantation and Results of Univariate Analysis

Prognostic Factor	*p*
Clinical	
Recipient's sex	0.296
Presence of hepatitis B surface antigen	0.413
Child-Pugh class other than C	0.004[a]
Serum α-fetoprotein level > 100 ng/mL at liver transplantation	0.045[a]
Period of disease prevalence[b]	N/A
Therapeutic	
History of surgical resection	0.312
History of interventional therapy	0.234
History of radiofrequency ablation/percutaneous ethanol injection therapy	0.861
History of transcatheter arterial chemoembolization	0.129
Period during which patients had untreated hepatocellular carcinoma	N/A
Type of liver transplantation	0.979
Radiologic	
No. of tumors > 3	0.030[a]
Diameter of largest tumor > 3 cm	0.002[a]
Sum of tumor diameters > 8 cm	0.022[a]
Viable tumor volume ratio > 10% after interventional therapy	0.030[a]
Bilobar distribution	0.502
Contact between tumor and hepatic capsule	0.115
Infiltrative tumor margin	0.113
Presence of intrahepatic portal venous thrombosis[c]	0.004[a]
Presence of collateral vessels (> 5 mm) due to portal hypertension	0.228
Presence of lymphadenopathy	0.093

Note—N/A = not available ($p > 0.05$ in all values tested).
[a]Statistically significant, log-rank test.
[b]From initial diagnosis of hepatocellular carcinoma to liver transplantation.
[c]In first- and second-order branches of portal vein regardless of contrast enhancement of thrombus itself.

pathologic reports to ascertain that the CT diagnoses of hepatocellular carcinoma were correct.

Liver Transplantation, Surgical Resection, and Interventional Therapy

In cases in which patients chose liver transplantation for the management of hepatocellular carcinoma, the only contraindication during our study period was the presence of extrahepatic involvement of hepatocellular carcinoma (i.e., imaging evidence of distant metastasis or evident tumor thrombus in the main portal vein or hepatic veins). We did not adhere to the Milan selection criteria (see Discussion) because we believed that these criteria were too stringent. Although lymphadenopathy measuring more than 1 cm was found in the drainage pathway on CT, this finding was not considered a contraindication to liver transplantation because the finding also can be present in benign hyperplasia. Selection of the type of liver transplantation depended on the availability of a living or cadaveric donor for the patient at the time of surgery. Most patients who chose not to undergo liver transplantation underwent surgical resection for the management of hepatocellular carcinoma. The other patients underwent radiofrequency ablation, percutaneous ethanol injection, and transcatheter arterial chemoembolization. In some cases, radiofrequency ablation was used as an adjunct to surgical resection.

Analysis of Prognostic Factors

We examined and evaluated various data as potential prognostic factors for tumor recurrence after liver transplantation. These prognostic factors are summarized in Table 3. We evaluated the number, size, and lobar distribution of the tumor, contact between the hepatic capsule and the tumor, pattern of tumor margin (discrete or infiltrative), collateral vessels (> 5 mm) due to portal hypertension, and lymphadenopathy in the drainage pathway on CT. Filling defect only in the intrahepatic portion of a portal vein (first and second order branches) was considered portal venous thrombosis regardless of the contrast enhancement of the thrombus itself. Viable tumor volume ratio after interventional therapy was assessed as the ratio of viable portion to entire tumor with the following formula: sum of volumes of portions of tumor exhibiting contrast enhancement divided by the sum of volumes of the contrast-enhanced portions plus the sum of volumes of the iodized oil–retained portions in cases of transcatheter arterial chemoembolization or the volumes of necrotic unenhanced portions in cases of radiofrequency ablation and percutaneous ethanol injection therapy. One radiologist using a 2,000 × 2,000 PACS (Centricity, GE Healthcare) screen with maximum magnification performed the measurements with an area measuring tool and summation-of-areas technique [19, 20] on images obtained during the hepatic arterial phase of the last follow-up CT examination before liver transplantation. CT analysis for prognostic factors other than volume measurement was performed in consensus by two abdominal radiologists with 7 and 23 years of experience in liver CT interpretation.

Statistical Analysis

After review of the follow-up CT scans after liver transplantation, we assessed the incidence of tumor recurrence and the cumulative disease-free survival rate. Cumulative disease-free survival rate was estimated with the Kaplan-Meier method. Significance of the prognostic factors was evaluated by univariate analysis with a log-rank test. In the log-rank test, representative values were used to categorize the data for the continuous variables. For instance, viable tumor volume ratio was categorized in terms of 10% units from 10% to 90%. We tested all values to determine which were significant. If multiple risk factors proved significant with this test, we performed multivariate analysis using a stepwise Cox hazards model to search for independently significant factors. Statistical significance was considered $p < 0.05$. Data analyses were performed with SPSS for Windows (version 11.0, SPSS).

Analysis of Cases with Recurrent Tumors

In cases in which recurrent hepatocellular carcinoma was found after liver transplantation, we investigated the number and location of the recurrent tumors, management of the tumors, disease processes after treatment, and mortality rates.

Results

After liver transplantation, regular follow-up evaluations were performed on all patients. The median and mean follow-up periods were 17.2 and 23.8 months, respectively (range, 2.0–102.4 months). The interval between the last CT examination in which prognostic fac-

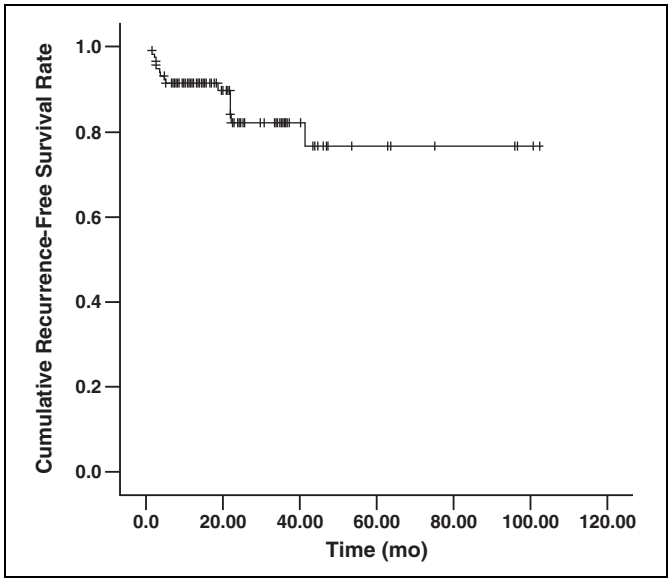

Fig. 1—Graph shows Kaplan-Meier survival curve for recurrence of hepatocellular carcinoma after liver transplantation. One-, 3-, and 5-year cumulative recurrence-free survival rates are 91.4%, 82.1%, and 76.6%, respectively. + = censored data.

TABLE 4: Results of Multivariate Analysis of Prognostic Factors for Hepatocellular Carcinoma Recurrence After Liver Transplantation

Factor	No. of Cases	Standard Error	Chi-Square Result	*p*	Risk Ratio
Portal venous thrombosis					
Presence	14	0.614	8.797	0.003[a]	6.024
Absence	105				1
Diameter of largest tumor					
> 3 cm	32	0.529	17.674	< 0.001[a]	4.082
≤ 3 cm	87				1
Viable tumor volume ratio after interventional therapy					
> 10%	26	0.387	21.707	< 0.001[a]	3.232
≤ 10%	92				1

[a]Statistically significant, stepwise Cox hazards model.

tor analysis had been performed and liver transplantation was 27.1 ± 19.5 days (mean ± SD) with a range of 0–81 days.

Incidence and Patterns of Recurrent Hepatocellular Carcinoma

Recurrent tumors were found in 16 (13.4%) of 119 patients. In seven (43.8%) of these cases, histopathologic examination of biopsy specimens confirmed the presence of lesions in the liver ($n = 4$), liver and skin ($n = 1$), abdominal wall ($n = 1$), and lung ($n = 1$). In five (31.3%) of the 16 cases, findings on sonography and contrast-enhanced multiphase CT were compatible with hepatocellular carcinoma. In four cases, recurrence was found in an organ other than the liver (lungs in two cases, lymph nodes in two cases) and was considered metastasis with appropriate radiologic features (interval increase in size of the tumor with doubling time compatible with malignancy) [21]. None of the patients with recurrent hepatocellular carcinoma had other underlying malignant diseases through the end of their follow-up periods.

Patterns of initial recurrence varied. The distribution of the tumors was disseminated (> 10 foci) in eight patients, multifocal in three patients (one with two foci in the liver, one with three foci in the lung, and one with four foci in the liver and spine), and solitary in five patients (two with a tumor in the liver, two with a lymph node tumor, and one with a tumor in a lung). The organs in which tumors initially presented also were diverse. The liver ($n = 11$) was the organ most frequently involved initially, followed by lymph nodes ($n = 6$), lung ($n = 4$), bone ($n = 2$, spine and rib), brain ($n = 1$), abdominal wall ($n = 1$), and skin ($n = 1$). Only four patients had recurrent tumors confined to the liver at initial diagnosis. The locations of recurrent tumors in the other 12 patients were both intrahepatic and extrahepatic in seven patients and extrahepatic only in five patients.

Disease-Free Survival Rates and Prognostic Factors

Time to development of recurrence ranged from 0.8 to 41.5 months after liver transplantation. The 1-, 3-, and 5-year cumulative disease-free survival rates according to the Kaplan-Meier method were 91.4%, 82.1%, and 76.6%, respectively (Fig. 1). The mean duration of recurrence-free survival was 83.0 months (95% CI, 73.2–92.7 months).

Univariate analysis with the log-rank test revealed the following prognostic factors were significant (Table 3): serum α-fetoprotein level > 100 ng/mL ($p = 0.045$), Child-Pugh class other than C ($p = 0.004$) (which means patients with more advanced cirrhosis fared better than those with better-compensated disease), presence of intrahepatic portal venous thrombosis ($p = 0.004$), presence of more than three tumors ($p = 0.030$), greater than 3-cm diameter of largest tumor ($p = 0.002$), greater than 8-cm sum of tumor diameters ($p = 0.022$), and viable tumor volume ratio after interventional therapy greater than 10% of entire tumor volume ($p = 0.030$). Multivariate analysis with a stepwise Cox hazard model revealed the following prognostic factors were independently statistically significant (Table 4): presence of intrahepatic portal venous thrombosis, greater than 3-cm diameter of largest tumor, and viable tumor volume ratio after interventional therapy greater than 10% of the original tumor.

Management and Prognosis of Recurrent Hepatocellular Carcinoma

We administered locoregional therapy to five patients with a solitary recurrent tumor. Radiofrequency ablation was performed on one patient with a solitary recurrent tumor in the liver. Excision of the metastatic lesion was performed on two patients, each with a solitary

recurrent tumor in the liver and metastatic lesion in the lung. Two patients with lymph node metastasis were treated with radiation therapy. The patients with multifocal or disseminated metastatic lesions underwent systemic chemotherapy or transcatheter arterial chemoembolization, depending on the distribution of disease.

Two patients with a single lymph node metastatic lesion had a good response to radiation therapy. They survived for 48.9 months and 7.2 months after liver transplantation (end of study period) without disease progression. The largest dimension of the lymph node lesions decreased from 2.5 to 0.3 cm and from 2.2 to 0.2 cm, respectively, after radiation therapy (Fig. 2). Three patients with a solitary recurrent tumor in the liver or lung treated with radiofrequency ablation or excision of a metastatic lesion had disease progression in a multifocal or disseminated form. Disease in the patients with multiple recurrent tumors worsened despite systemic chemotherapy or transcatheter arterial chemoembolization. At the end of the study period, one (20%) of five patients with a single recurrent tumor and eight (72.7%) of 11 patients with multiple recurrent tumors had died 6 days–22.6 months after the initial diagnosis of recurrence. The overall mortality rate among the patients with recurrent hepatocellular carcinoma after liver transplantation was 56.3% (9/16). According to the Kaplan-Meier method, the 1- and 2-year survival rates calculated from the time of initial diagnosis of recurrent hepatocellular carcinoma were 44.1% and 29.4%, respectively. The mean and median durations of survival were 13.4 and 7.1 months (95% CI, 7.8–19.0 and 5.5–8.7 months).

Discussion

Patients with large, unresectable hepatocellular carcinomas, especially tumors originating in a noncirrhotic liver, once were considered the most appropriate group for liver transplantation [22]. As experience has accumulated, however, it has become clear that tumor burden is the most important prognostic factor for recurrence of hepatocellular carcinoma after liver transplantation. Several studies [2, 23–28] have shown low recurrence and excellent survival rates when liver transplantation has been restricted to patients with tumors small in size and number. Many transplantation programs have adopted the Milan selection criteria [27, 28], which are that a solitary hepatocellular carcinoma 5 cm or less in diameter and multiple hepatocellular carcinomas with three or fewer foci and measuring 3 cm or less in diameter can be managed with liver transplantation.

Significant factors for poor prognosis other than the number and size of the tumors have been reported by many investigators. These factors include microscopic vascular invasion by the tumor [3–7], poor histologic differentiation [8, 9], presence of a microscopic peritumoral capsule [10], presence of partial necrosis of the nodule in the explanted specimen [11], presence of microscopic satellite nodules in the explanted specimen [12], allelic loss of heterozygosity for various tumor suppressor genes [13], specific type of lymphocytic infiltrate to the tumor as immune response [14], immunosuppressive regimen after liver transplantation [15], high preoperative level of serum α-fetoprotein [16], and advanced TNM stage [17, 18]. Even though some of these factors, such as serum α-fetoprotein level, are controversial [10], all but the last two can be documented only after liver transplantation by use of histopathologic and genetic analysis of the explanted specimen or of clinical data after liver transplantation. This problem is especially evident in some centers reluctant to perform percutaneous biopsy before liver transplantation for fear of tumor seeding. Prognostic factors related to certain therapeutic techniques have greater clinical implication when they can be used for prognosis of clinical outcome before therapy is initiated. This fact adds value to our study, which dealt with exclusively preoperative data as prognostic factors.

Recurrence of hepatocellular carcinoma after liver transplantation is common, the reported recurrence rate being as high as 40% [2]. However, in cases in which the Milan selection criteria were adopted, risk of recurrence decreased to 10–15% at 5 years [12, 28]. In our study, the cumulative recurrence rate at 5 years was 23.4%, higher than the rates in studies in which the Milan criteria were used. Reviewing our data on the size and number of the tumors, were found that not a few (44/119, 37%) of the cases did not fulfill the Milan selection criteria at the time of transplantation. This finding may be a reasonable explanation for the higher recurrence rate. Recurrence patterns in our study also were not very different from those in previous studies. In our study, the organ most frequently involved initially was the liver; in other studies [10, 17], it was the liver or lung.

As the proportion of transplantation procedures performed with living donors increases, the preoperative waiting time is being shortened, and delays in surgery are not as important as they were in the past. We cannot, however, deny that disease progression occurs during this waiting time. Several studies have addressed the role of systemic and locoregional therapies during the waiting period. In one study, the investigators [29] found that radiofrequency ablation was safe and effective therapy for small hepatocellular carcinomas in patients with cirrhosis awaiting liver transplantation. More recent studies [30, 31] showed that aggressive multimodal therapies, including locoregional therapy and systemic chemotherapy, reduced the rate of recurrence of hepatocellular carcinoma after liver transplantation. Our result that more than 90% reduction of viable tumor volume with interventional therapy prevented tumor recurrence after liver transplantation supports the positive role of adjuvant therapies. This result is in accordance with the previous finding that a large tumor burden is a poor prognostic factor in that viable tumor volume in treated cases may be analogous to tumor burden in untreated cases. Another possible explanation is that tumors with a good response to interventional therapy have a favorable biologic nature, which contributes to a better prognosis. Two independently significant poor prognostic factors—greater than 3-cm diameter of the largest tumor and presence of intrahepatic portal venous thrombosis on CT—in our study were supportive of previous findings that tumor burden and microvascular invasion on pathologic specimens are poor prognostic factors. In a case of intrahepatic portal venous thrombosis, although we did not correlate the findings with pathologic specimens, the presence of a filling defect in an intrahepatic portion of the portal vein on contrast-enhanced CT regardless of contrast enhancement of the filling defect itself may suggest the possibility of a vascular invasion by the tumor.

All prognostic factors that turned out to be independently significant in our study seem to be supportive or repetitive of results in previous studies. However, whereas previous studies included preoperative and postoperative data, and identification of risk factors from imaging was not the focus, the data analyzed in our study were obtained exclusively with preoperative procedures, especially radiologic studies. We believe the method of data collection is the original aspect of our study in that the data are the type used in the clinical setting

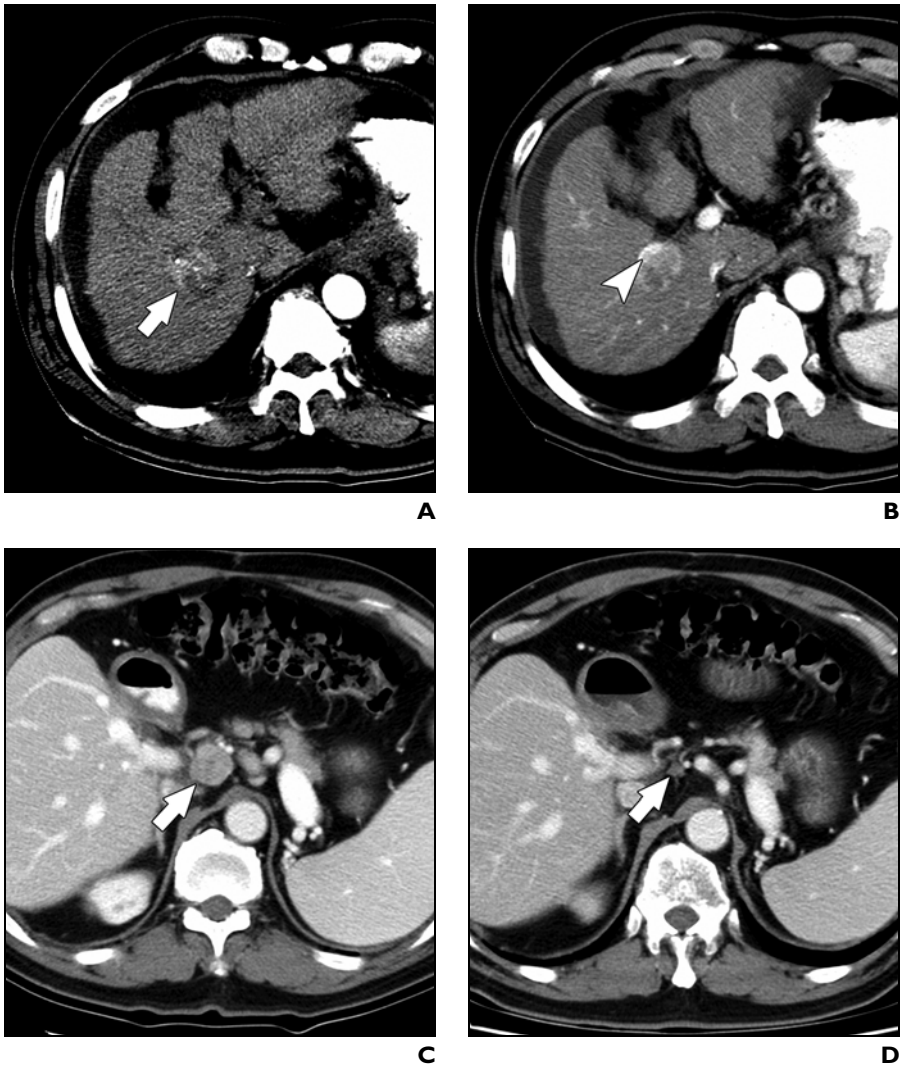

Fig. 2—53-year-old man with stable disease after radiation therapy for recurrent hepatocellular carcinoma after liver transplantation and with hepatitis B–related liver cirrhosis in Child-Pugh class B.
A and **B,** Contrast-enhanced CT scans show 3-cm hepatocellular carcinoma (*arrow,* **A**) in right hepatic lobe with right intrahepatic portal vein invasion (*arrowhead,* **B**) managed with living-donor liver transplantation.
C, Contrast-enhanced CT scan shows solitary recurrent tumor found in celiac lymph node (*arrow*) approximately 22 months after liver transplantation.
D, Contrast-enhanced CT scan after radiation therapy shows considerable decrease in size of celiac lymph node (*arrow*). Patient survived in stable condition for 48.9 months after transplantation.

of planning liver transplantation in the management of hepatocellular carcinoma.

Justification of interventional therapy before liver transplantation is controversial because radiofrequency ablation and percutaneous ethanol injection therapy and transcatheter arterial chemoembolization may be responsible for tumor recurrence after liver transplantation as the result of mechanical tumor spread and possible promotion of angiogenesis, respectively. In cases of radiofrequency ablation, we adopted several strategies to minimize possible tumor seeding. These strategies include use of the fewest possible tumor punctures, avoidance of direct tumor puncture (i.e., establishment of the parenchymal electrode pathway before tumor puncture), and tract ablation during electrode withdrawal. In our population, neither univariate nor multivariate analysis yielded statistical evidence of increased risk of tumor recurrence from interventional therapy before liver transplantation.

In general, recurrence of hepatocellular carcinoma after liver transplantation is considered to result from undetected extrahepatic metastasis before surgery or the release of tumor cells during surgical manipulation [2, 7]. On the basis of this concept, we can assume that patients with recurrent hepatocellular carcinoma after liver transplantation may have a poor prognosis because the emergence of recurrent hepatocellular carcinoma means malignant cells have already spread beyond the liver and are present in other parts of the body. We ascertained as much in our study. The mortality among patients with recurrent hepatocellular carcinoma was high (56.3%), especially among patients with multiple lesions (72.7%). Although recurrence was solitary and managed with locoregional therapies, all of these patients other than those with solitary lymph node recurrence eventually had disease progression. As far as we know, there has been no well-organized analysis of the long-term results of locoregional therapy for solitary recurrence of hepatocellular carcinoma after liver transplantation. In the cases of lymph node recurrence, in which the lesions decreased in size after radiation therapy over a long follow-up period, we assumed that different types of pathogenetic mechanisms were at work.

Our study had the following limitations: First, we reviewed the cases retrospectively. Second, although the contrast-enhancement protocol for CT examinations, such as the iodine concentration of contrast medium and injection rate, was standardized, our method may not be ideal for imaging hepatocellular carcinoma. Third, our analysis of prognostic factors with only CT data, rather than pathologic data, may have yielded findings different from the actual pathologic status. Our reason for adopting this method was to comply with the purpose of the study, which was to evaluate the utility of various CT findings in the prognosis of clinical outcome among patients with recurrent tumors. Therefore, we were intentionally blinded to the results of the pathologic reports.

In conclusion, tumor recurrences after liver transplantation for unresectable hepatocellular carcinoma are not rare, and the prognosis is unfavorable. It is desirable to narrow the indications for liver transplantation for hepatocellular carcinoma to tumors with the contrast-enhanced CT findings of small size (3 cm or less) and absence of portal venous thrombosis. If the tumor is larger than 3 cm, aggressive interventional therapy is highly recommended to minimize viable tumor burden before transplantation.

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