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Letter to the Editor

Surgery versus radiofrequency ablation for small hepatocellular carcinoma: Start of a randomized controlled trial (SURF trial)

Dear Editor,

"Which is more effective as an initial treatment for small hepatocellular carcinoma (HCC), hepatectomy or percutaneous ablation therapy?" This has been one of the most significant questions in the domain of hepatology. In spite of the recent results of two randomized controlled trials (RCT)[1,2] and a prospective nationwide cohort study conducted by the Liver Cancer Study Group of Japan,[3,4] their implications cannot be accepted as conclusive, because each of them had some severe problems.

Meanwhile, a multicenter joint study (abbreviated to SURF trial after surgery vs radiofrequency ablation) is being done in Japan to reach a strong conclusion to the question cited above. The major qualifications for the subjects of this study are: (i) tumor conditions (initial HCC exhibiting typical findings on diagnostic images, tumor foci numbering three or fewer, and each measuring 3 cm or less); (ii) conditions for hepatic functions (Child–Pugh score of 7 or less); (iii) aged between 20 and 79 years; and (iv) indications for either hepatectomy or radiofrequency ablation (RFA) for the treatment which are decided at each hospital. In Japan, there were a few studies of a similar nature planned in the past but none were completed. In reflection on the earlier failures, innovations are made for the following in the current study.

1 We adopted two co-primary end-points: overall survival and recurrence-free survival. When deciding on the primary end-point in this trial, an opinion was expressed that, "Since more than one effective method of treatment is available for a recurrence, the efficacy of the initial treatment for HCC tends to diminish. Moreover, recurrences are better for directly evaluating therapeutic efficacy itself", but there was also an opinion that "even if there are many recurrences in the early stage, because RFA is less invasive than liver resection, there is less of an impact on liver function, and treatment after recurrence can also be performed easily, the survival rate may be better. After all, if overall survival is not examined, there is no point", as well as an opinion that, "Both recurrence and survival should be looked at", and it was the most heatedly debated issue. While it is true that, theoretically, overall survival is the true end-point from the standpoint of evaluating treatment methods,[5] in order to reduce the sample size, shorten the follow-up period and increase the possibility of completion, we decided to also use recurrence-free survival as a primary end-point. In the present study, a total of 600 cases are needed to find a 10% difference, assuming 3-year recurrence-free survival rates following hepatectomy and RFA of 45% and 35%, respectively (University of Tokyo Hospital, 2008). According to the same database, the 5-year overall survival rates of the two therapeutic modalities are approximately 70%. If the results of either therapeutic method are to fall around this figure, it is also statistically confirmed that 600 cases would be sufficient to detect a difference of 10% in overall survival. The current study is designed so that a 10% difference can be detected between surgery and RFA both in the overall and recurrence-free survival rates, thus it is appropriate to use these two as the primary end-points.

2 The primary purpose of this study is to compare and evaluate the two therapeutic methods by employing an RCT format; but considering that there may be a number of patients who do not wish to participate in the RCT, a parallel prospective cohort study is planned. Those patients who meet the requirements of RCT but decline to participate in the RCT will be registered upon their consent and they will be followed up after either surgery or RFA selected by themselves. It is anticipated that through this cohort study, valuable data would be obtained in interpreting and extrapolating the results of RCT. We have to emphasize that the subjects of this cohort study are unique in that they are true double candidates for surgery and RFA confirmed by both surgeons and gastroenterologists at each institute before registration.

3 In January 2007, the Departments of Hepato–Biliary–Pancreatic Surgery, Gastroenterology and Radiology of University of Tokyo Hospital jointly prepared a

draft for a protocol with the biological statistician, after which the representatives of 13 facilities with ample experience in the related treatment joined to evaluate the plan. Thorough discussions took place during three study meetings, while a survey by using questionnaires was conducted to find the status of RFA and surgery concerning HCC. It required approximately 22 months before a skeleton of the protocol was completed; but by exposing the plan to specialists in various disciplines, we believe that it became a protocol that even other facilities can readily accept. An outline of the final version of the protocol has been registered at UMIN-CTR (www.umin.ac.jp/ctr/index.htm) for public examination (Registration ID: UMIN000001795 and 1796).

4 In order to ensure the quality of treatment performed at individual institutions, we made at least 20 cases a year the number of times of liver resection and RFA had to be performed in the conditions for participation. Although there is no strong basis for setting the number at 20, we thought that some sort of hurdle should be established so that patients would not be disadvantaged depending on whether they were assigned to one group or the other.

The SURF trial has been already started from 1 April 2009 with participation of more than 80 institutions throughout the country. The Japan Surgical Society, the Japan Society of Hepatology, and the Liver Cancer Study Group of Japan have officially approved the protocol of this trial. Thus, the SURF trial is now a Japanese national study. We are anxious for the day when the target number of patients are registered as planned and sound evidence is presented from Japan to the world.

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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Significance of Alpha-Fetoprotein and Des-γ-Carboxy Prothrombin in Patients with Hepatocellular Carcinoma Undergoing Hepatectomy

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ABSTRACT

Background. Alpha-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) are well-known tumor markers of hepatocellular carcinoma (HCC). The aims of this study are to calculate the sensitivity/specificity of AFP and DCP measurement for the diagnosis of HCC, measure response rates of the markers following curative-intent resections, determine the correlations between the marker levels and clinicopathological prognostic variables, and determine the correlations between the marker levels before hepatectomy and those at diagnosis of recurrence.

Methods. A retrospective cohort study of 714 consecutive patients with HCC undergoing hepatectomy was carried out.

Results. The areas under the receiver operating characteristic curves were 0.79 versus 0.91 for AFP and DCP, respectively ($P < 0.001$). Positive AFP and DCP status became negative at 6 months post surgery in 184/229 (80.3%) and 245/246 (99.6%) patients, respectively (cutoff values being 20 ng/ml for AFP and 40 mAU/ml for DCP; $P < 0.0001$). No correlation was found between marker levels ($rs = 0.23$). The level of DCP, but not that of AFP, showed a close correlation with tumor size ($rs = 0.51$ and 0.19, respectively). They were associated with indices of tumor invasiveness without showing any specific associations. AFP and DCP levels in patients showing recurrence in ≤6 months correlated with the levels measured before surgery ($rs = 0.78$ and 0.49, respectively) but not in those showing recurrence after 2 years ($rs = 0.31$ and 0.30, respectively).

Conclusions. DCP is a more accurate, albeit complementary, HCC marker than AFP. While the levels of both markers increased with advancing tumor growth, no specific associations were found. The marker values at recurrence indicated the type of recurrence.

Early diagnosis remains the key to effective therapy in cases of hepatocellular carcinoma (HCC). Although serum alpha-fetoprotein (AFP), a biological tumor marker of HCC, has long been used as a tool for HCC surveillance, it is not an ideal screening test due to its low sensitivity/specificity.[1–3] Liebman et al. first reported, in 1984, an increase in the plasma levels of des-γ-carboxy prothrombin (DCP), which is an abnormal prothrombin and also otherwise known as protein induced by vitamin K deficiency or antagonist-II (PIVKA-II), in patients with HCC.[4] Since then, the significance of DCP has been examined by many investigators and it was introduced as a routine laboratory test for HCC during the early 1990s in Japan.[5–7] In addition, a two-step enzyme immunoassay method was developed and has been in use since 1997; it shows a tenfold higher sensitivity for detection as compared with the conventional enzyme immunoassay method.[8] Consensus appears to have been reached on both DCP and AFP being independent tumor markers in HCC.[9–11] However, it still remains controversial whether or not DCP is superior to AFP as a single marker.[12–16]

The second role of tumor markers is in the monitoring of response to therapy. Ideally, the levels of tumor markers should fall to within normal range after effective treatment. This aspect is especially important in the case of

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transcatheter arterial embolization, because radiological findings do not necessarily reflect the degree of biological remission achieved by necrosis or fibrosis. Comparisons of AFP and DCP in this regard have not been conducted.

Thirdly, elevation of tumor marker levels reportedly represents specific clinicopathological variables identified as prognostic factors. Although high plasma levels of DCP reportedly indicate the presence of portal venous thrombosis and increased serum AFP levels are associated with a poor degree of differentiation of the tumor cells, in particular, these studies failed to comprehensively investigate the relationships with various parameters.

Finally, another use of tumor markers is in the prediction of tumor recurrence. In theory, patients with HCC with elevated levels of AFP and/or DCP before treatment should also show elevated levels of the respective markers at the time of recurrence if the recurrence is metastatic. On the other hand, de novo secondary tumors also contribute to postoperative intrahepatic HCC recurrence.

In the present study, taking into account these unaddressed aspects of tumor markers of HCC, we comprehensively investigated the clinical significance of measurement of two tumor markers in cases of HCC, i.e., AFP and DCP, in a large cohort.

PATIENTS AND METHODS

Patients

The base population consisted of 714 consecutive patients who underwent curative liver resections for HCC at the Division of Hepato-Biliary-Pancreatic Surgery, Tokyo University Hospital, between January 1998 and November 2006. Curative resection was defined as removal of all recognizable tumors with a clear margin. The diagnosis of HCC was finally confirmed by pathological examination of the resected specimens in all cases.

Background characteristics of the patients are presented in Table 1. After discharge, monthly follow-up by tumor markers (AFP and DCP) and ultrasound as well as dynamic computed tomography (CT) scan every 4 months were conducted for 1 year. Then, we screened patients by tumor marker measurement and ultrasound every 2 months and dynamic CT scan every 6 months thereafter. We defined recurrence as the appearance of new lesions with radiological features typical of HCC, as confirmed by at least two imaging methods.

AFP and DCP Assay

Samples for AFP and DCP were taken within 7 days prior to the liver resection. Serum AFP level was measured by commercially available immunometric assay (ST AIA-PACK AFP, Tosoh, Tokyo, Japan). Plasma DCP level was measured by two-step enzyme immunoassay (Picolumi PIVKA-II, Eizai, Tokyo, Japan).

TABLE 1 Background characteristics of 714 patients with HCC

Variables	$n = 714$
Sex	
Male	556 (77.9%)
Female	158 (22.1%)
Age (years)[a]	67 (19–90)
Hepatitis B virus infection[b]	
No	560 (78.4%)
Yes	154 (21.6%)
Hepatitis C virus infection[b]	
No	250 (35.0%)
Yes	464 (65.0%)
Child–Turcotte–Pugh grade[c]	
A	601 (84.2%)
B	113 (15.8%)
Background liver status[d]	
Normal liver	14 (2.0%)
Chronic hepatitis	295 (41.3%)
Cirrhosis	405 (56.7%)

[a] Median with range

[b] Five patients were positive for both hepatitis B and C virus infections and 101 patients were negative for both hepatitis B and C virus infections

[c] No patient was Child–Turcotte–Pugh grade C

[d] Pathological findings assessed in the resected specimen

Assessment

Sensitivity/Specificity of AFP and DCP for Presence of HCC At 6 months post surgery, 25 out of the 714 patients were lost to follow-up in terms of serial tumor marker measurements, 190 had developed recurrence, 9 were disease-free at <6 months of follow-up, and the remaining 490 patients were confirmed to be disease free at this time point. The AFP and DCP values in 714 patients before the liver resection were defined as those of patients with HCC, while the values of these 490 patients at 6 months post surgery were defined as those of patients without HCC. Using these values, receiver operating characteristic (ROC) curves were constructed. The diagnostic performance of AFP and DCP was evaluated and compared through their areas under the receiver operating characteristic curves (AUROC). The cutoff values for AFP and DCP used in this study are those that have been conventionally used and/or have been proposed in previous reports: 20 ng/ml for AFP and 40 mAU/ml for DCP.

AFP and DCP Levels as Tools for Evaluating Therapeutic Response to HCC In these 490 patients, complete tumor remission was thought to be achieved at 6 months after the liver resection. We examined whether this treatment response was correctly reflected in the alterations in the marker values. According to the cutoff values defined above, we classified the 490 patients into marker-positive or marker-negative status both before and at 6 months after the liver resection. We then investigated the changes of AFP- and DCP-positive/negative status following the liver resection.

AFP and DCP as Complementary Tumor Markers for HCC We first evaluated the relationship between AFP and DCP values in a total of 714 patients. Second, we classified these patients into four categories according to their positive/negative status for AFP and/or DCP according to the cutoff values.

AFP and DCP as Markers of Clinicopathological Variables Representative of Tumor Invasiveness and Prognosis We assessed the association of AFP and DCP values with clinicopathological variables that have been reported as prognostic factors for HCC in the 714 patients. The variables investigated are shown in Table 2. All variables were assessed pathologically on the resected specimens. Vascular invasion was defined as presence of portal vein invasion, venous invasion or biliary invasion. Multiple primary tumor nodules and intrahepatic metastases were differentiated using the guidelines proposed by the Liver Cancer Study Group of Japan.[11]

AFP and DCP Levels as Indices for Predicting the Pattern of Recurrence At the time of data collection, recurrence was observed in 444 patients. We classified these patients with recurrence into two groups, i.e., a group in which the recurrence occurred ≤6 months post surgery ($n = 190$),

TABLE 2 Tumor-related factors

Variables	$n = 714$	AFP (ng/ml)[a]	DCP (mAU/ml)[a]
Tumor size (mm)			
≤20	223 (31.2%)	18.0 (7.0–69.0)	24.0 (16.0–61.0)
20–50	335 (46.9%)	22.0 (7.0–144.0)	57.0 (21.0–328.0)
>50	156 (21.9%)	57.0 (8.5–3007)	1251.0 (118.5–7486.0)
		$rs = 0.19$	$rs = 0.51$
Tumor number			
1	483 (67.7%)	19.0 (1.0–216.0)	55.0 (20.0–456.0)
2	138 (19.3%)	26.0 (8.0–177.5)	53.0 (19.50–254.0)
≥3	93 (13.0%)	49.0 (13.5–162.5)	59.0 (19.5–329.5)
		$P = 0.07$	$P = 0.73$
Capsular formation			
No	169 (23.7%)	25.0 (8.0–148.0)	32.0 (18.0–163.0)
Yes	545 (76.3%)	21.0 (7.0–207.5)	72.0 (21.0–489.5)
		$P = 0.83$	$P < 0.05$
Capsular infiltration[b]			
No	137 (25.1%)	14.0 (6.0–78.5)	64.0 (10.0–364.0)
Yes	408 (74.9%)	27.0 (7.0–278.0)	83.5 (21.5–579.5)
		$P < 0.01$	$P = 0.21$
Vascular invasion[c]			
No	495 (69.3%)	17.0 (7.0–76.0)	38.0 (18.0–189.0)
Yes	219 (30.7%)	88.0 (12.0–1271.0)	233.0 (31.0–2110.0)
		$P < 0.0001$	$P < 0.0001$
Intrahepatic metastases			
No	601 (84.2%)	19.0 (7.0–137.0)	44.0 (10.0–310.5)
Yes	113 (15.8%)	81.0 (9.5–1261.0)	235.0 (40.0–2544.0)
		$P < 0.001$	$P < 0.0001$
Tumor differentiation			
Well	104 (14.5%)	12.5 (6.0–31.0)	29.0 (17.0–87.5)
Moderate	511 (71.6%)	20.0 (1.0–174.0)	63.0 (10.0–441.0)
Poorly	99 (13.9%)	165.0 (25.0–2326.0)	145.0 (26.0–2455.0)
		$P < 0.0001$	$P < 0.0001$

[a] Median with interquartile range

[b] We assessed 545/714 patients who had capsular formation

[c] Macroscopic invasion was observed in 45/219 (20.5%) patients, while microscopic invasion was found in 174/219 (79.5%) patients

and another in which the recurrence occurred >6 months post surgery ($n = 254$). We first compared the preoperative levels of AFP and DCP as well as the levels at time of recurrence between the two groups of patients. Then, we further classified the two groups of patients into two subgroups according to site of recurrence, i.e., intrahepatic or extrahepatic recurrence. We investigated the correlations between the preoperative marker values and the site of recurrence.

Etiological Association Between the Primary and Recurrent Tumors Investigated Through AFP and DCP Marker Values We investigated the correlations of the tumor marker values at the time of recurrence with those measured before the liver resection. We classified 444 patients who developed recurrences into four groups according to time to recurrence, as follows: recurrence at ≤6 months ($n = 190$), recurrence between 7 and 12 months ($n = 70$), recurrence between 13 and 24 months ($n = 70$), and recurrence after 2 years ($n = 114$). Then, we examined the chronological alterations in the correlation of values of the respective tumor markers measured before the liver resection with those measured at the time of recurrence.

Statistical Analysis

Marker values are expressed as median with interquartile range. The AUROC for markers was compared by Wilcoxon's rank-sum test. Correlations between marker values were analyzed by Spearman's rank correlation. Categorical binary variables were compared by Fisher's exact test. Associations between marker values and clinicopathological variables were analyzed by Wilcoxon's rank-sum test or by the Kruskal–Wallis test, as appropriate. P values of < 0.05 were accepted as statistically significant. All statistical analyses were performed using the GraphPad Prism® computer software, version 5 (GraphPad Software Inc., San Diego, CA).

RESULTS

Sensitivity/Specificity of AFP and DCP for Presence of HCC

The median (interquartile range) AFP and DCP levels in 714 patients before liver resection were as follows: 22.0 (7.0–195.0) ng/ml and 55.0 (20.0–443.0) mAU/ml. The AFP and DCP levels in 490 patients who had no evidence of tumor recurrence at 6 months post surgery were 5.0 (3.0–9.0) ng/ml and 11.0 (10.0–15.0) mAU/ml, respectively. The sensitivity and specificity of AFP and DCP were assessed by ROC curves (Fig. 1). The AUROC (95% confidence interval, CI) for AFP and DCP were 0.79 (0.76–0.81) and 0.91 (0.89–0.92), respectively ($P < 0.001$). The sensitivities and specificities at various cutoff values including those adopted in the present study (AFP, 20 ng/ml; DCP, 40 mAU/ml) and proposed in previous reports are presented in Table 3.

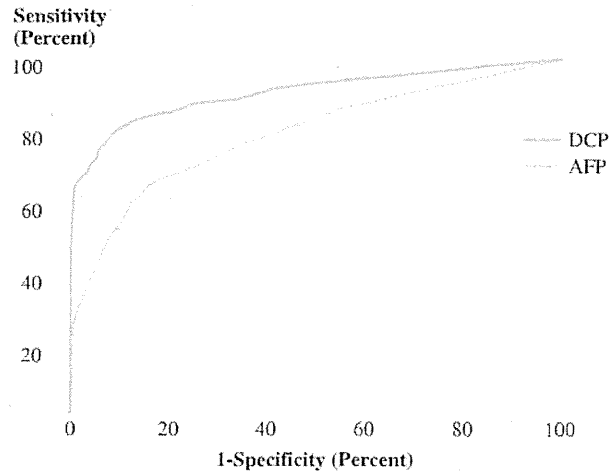

FIG. 1 ROC curves for AFP and DCP. The yellow line represents AFP and the blue line represents DCP. The AUROC (95% CI) for AFP and DCP were 0.79 (0.76–0.81) and 0.91 (0.89–0.92), respectively ($P < 0.001$)

TABLE 3 Sensitivities and specificities of AFP and DCP values according to various cutoff values

AFP (ng/ml)	11	13	20	100	200
Sensitivity (%)	64.9	60.8	51.3	30.4	24.7
Specificity (%)	82.9	86.1	90.8	98.6	99
DCP (mAU/ml)	20	30	40	100	125
Sensitivity (%)	73.4	62.8	55.9	41.9	39.1
Specificity (%)	94.7	99.4	99.8	100	100

In the present study, the cutoff values adopted were 20 ng/ml for AFP and 40 mAU/ml for DCP

AFP alpha-fetoprotein, *DCP* des-γ-carboxy prothrombin

AFP and DCP as Tools for Evaluating Response to Therapy of HCC

Among the 490 patients who were confirmed to be disease free at 6 months postoperatively, 229 (46.7%) and 246 (50.2%) were classified as AFP positive and DCP positive, respectively, before the liver resection under the present cutoff values. At 6 months post surgery, when complete tumor remission was thought to have been achieved, marker-negative status was achieved in 184/229 (80.3%) and 245/246 (99.6%) patients for AFP and DCP, respectively ($P < 0.0001$) (Table 4). Out of 45 patients

TABLE 4 Pre- and postoperative marker status in 490 disease-free patients at 6 months

Preoperative status		Postoperative status	
AFP			
(+)	229/490 (46.7%)	(−)	184/229 (80.3%)
		(+)	45/229 (19.7%)
(−)	261/490 (53.3%)	(−)	261/261 (100%)
		(+)	0/261 (0%)
DCP			
(+)	246/490 (50.2%)	(−)	245/246 (99.6%)
		(+)	1/246 (0.4%)
(−)	244/490 (49.8%)	(−)	244/244 (100%)
		(+)	0/244 (0%)

Cutoff values were set at 20 ng/ml for AFP and 40 mAU/mL for DCP, respectively

AFP alpha-fetoprotein, *DCP* des-γ-carboxy prothrombin

who showed AFP-positive status without recurrence at 6 months post surgery, 33 remained disease free at 12 months post surgery, whereas 12 had developed recurrence by this time point. In retrospect, the AFP values at 6 months post surgery were not thought to be indicative of recurrence at least in 6/12 patients. A single patient positive for DCP at 6 months post surgery was also disease free 5 years later. In all the 261 (53.3%) and 244 (49.8%) patients who were negative for AFP and DCP, respectively, before the surgery, the marker status for both of these markers remained negative at 6 months post surgery (Table 4).

AFP and DCP as Complementary Tumor Markers for HCC

The correlation between the levels of these markers in the 714 patients is shown in Fig. 2; no association was seen ($rs = 0.23$). These patients were classified into four categories by the cutoff values used in the present study, as follows: AFP(+)/DCP(+): 229 (32.1%), AFP(+)/DCP(−): 137 (19.2%), AFP(−)/DCP(+): 170 (23.8%), and AFP(−)/DCP(−): 178 (24.9%) (Fig. 2).

AFP and DCP as Markers of Clinicopathological Variables Representative of Tumor Invasiveness and Prognosis

The correlations of the AFP and DCP levels with clinicopathological findings are shown in Table 3. Although the DCP levels increased with increasing tumor size ($rs = 0.51$), this relationship was not found for AFP ($rs = 0.19$). While no statistical correlation was found between DCP levels and tumor number ($P = 0.73$), AFP levels tended to increase with increasing tumor number

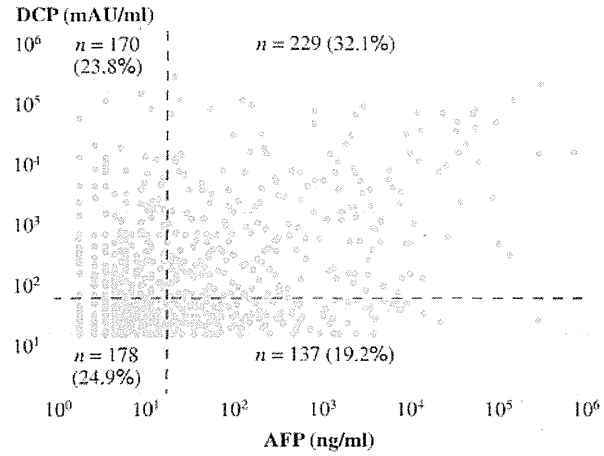

FIG. 2 Correlation between AFP and DCP values in 714 patients. No correlation was found between the two markers ($rs = 0.23$, $P < 0.0001$). Dotted line represents cutoff values, i.e., 20 ng/ml for AFP and 40 mAU/ml for DCP. Patients were placed into four categories: either positive or negative for AFP and/or DCP according to these cut-off values. Number of patients in the each category was shown

($P = 0.07$). AFP and DCP levels increased to similar extent in the presence of indices of tumor invasiveness, such as vascular invasion and intrahepatic metastases. Likewise, both marker levels increased with increasing tumor cell differentiation.

AFP and DCP Levels as Indices for Predicting the Pattern of Recurrence

The preoperative AFP and DCP values in HCC patients who developed recurrence ≤6 months ($n = 190$) versus patients who developed recurrence >6 months post surgery ($n = 254$) are shown in Table 5. Patients who developed recurrence ≤6 months post surgery showed higher preoperative AFP and DCP values than those who developed recurrence >6 months post surgery. Similarly, the AFP and DCP values measured at the time of recurrence in the two groups are shown separately in Table 5. Again, patients who developed HCC recurrence ≤6 months post surgery showed higher AFP and DCP values at the time of recurrence.

Out of 190 recurrences observed ≤6 months post surgery, 32 (16.8%) were extrahepatic: 18/32 (59 %) in the lung, 6/32 (19%) in the lymph node, 4/32 (13%) in the bone, 2/32 (6%) in the peritoneal membrane, and 1/32 (3%) in the adrenal gland.

On the other hand, the overall rate of extrahepatic recurrence in the patients who developed recurrence >6 months post surgery was 3/254 (1.2 %). Since extrahepatic recurrence was a rare event >6 months post surgery, we analyzed the correlations between the

TABLE 5 AFP and DCP values in patients who developed HCC recurrence ≤6 months ($n = 190$) and >6 months ($n = 254$) post surgery

	Preoperative values		Values at recurrence	
	Recurrence ≤6 months	Recurrence >6 months	Recurrence ≤6 months	Recurrence >6 months
AFP (ng/ml)	54.0 (9.0–624.5)[a]	18.5 (7.0–76.0)	17.5 (6.0–163.5)[a]	13.0 (6.0–43.0)
DCP (mAU/ml)	237.5 (22.8–2553.0)[b]	37.5 (19.0–142.0)	25.0 (14.0–131.0)[c]	18.0 (13.0–34.3)

Values are expressed as median (interquartile range)

[a] $P < 0.0001$ compared with recurrence >6 months

[b] $P < 0.005$ compared with recurrence >6 months

[c] $P < 0.0005$ compared with recurrence >6 months

TABLE 6 Preoperative AFP and DCP values in patients who developed intrahepatic ($n = 158$) and extrahepatic ($n = 32$) recurrence ≤6 months post surgery

	Intrahepatic recurrence	Extrahepatic recurrence
AFP (ng/ml)	50.0 (9.0–337.8)[a]	255.0 (10.8–9636.0)
DCP (mAU/ml)	188 (22.8–184.0)[b]	543.0 (34.3–10179.0)

Values are expressed as median (interquartile range)

One patient who developed intra- and extrahepatic recurrences simultaneously was classified into those with extrahepatic recurrence

[a] $P < 0.05$ compared with extrahepatic recurrence

[b] $P = 0.08$ compared with extrahepatic recurrence

preoperative marker values and the site of recurrences exclusively in the 190 patients who developed recurrence ≤6 months post surgery (Table 6). Patients who developed intrahepatic recurrence ($n = 158$) showed higher preoperative marker values than those who developed extrahepatic recurrence ($n = 32$).

AFP and DCP as Markers Reflecting the Association Between the Primary and Recurrent Tumors

The values of AFP and DCP measured before the liver resection are plotted against the values measured at the time of recurrence separately according to their time to recurrences in Fig. 3A–D and Fig. 4A–D, respectively. The AFP values in patients with recurrence at ≤6 months showed a close relationship with those measured before the liver resection ($rs = 0.78$, Fig. 3A). The strength of this relation became weaker in the groups with longer time to recurrence (Fig. 3B–D).

A similar trend was found in regard to the relationship of DCP values, although the correlations were weaker than those observed for AFP (Fig. 4A–D).

DISCUSSION

The diagnostic accuracy of tumor markers should be evaluated on the basis of a trade-off between sensitivity and specificity, ideally by drawing ROC curves.[1] To date, three cross-sectional studies have compared the accuracy of AFP and DCP levels for the diagnosis of HCC through ROC curves, each using the present sensitive assay method for measuring DCP.[17,19,20] Two studies reported superiority of DCP.[17,20] However, a third reported better overall diagnostic accuracy of AFP.[19] The distribution of the etiology of the underlying liver disease in the present study population was similar to that in the populations studied by Marrero et al. and Nakamura et al., except that the former included a quantifiable proportion of alcoholic patients.[19,20] In regard to the distribution of the Child–Turcotte–Pugh (CPT) grade, our cohort is thought to lie in between the study cohorts of Marrero et al. and Nakamura et al., since 84.2% of our patients were classified into CPT grade A.[19,20]

In this study, we defined patients without recurrence at 6 months post surgery as a cohort without HCC. Although this approach may be different from that of former studies, this is advantageous in that the background characteristics are uniform in the patients with and without HCC.[19,20] This situation, which is an essential requirement in prospective screening studies of tumor markers, is not necessarily guaranteed in a cross-sectional study.[2] This study showed similar ROC results to those reported by Marrero et al. and Wang et al., which demonstrated superiority of DCP by approximately 10% (0.73–0.83 versus 0.85–0.93 for AFP versus DCP) (Fig. 1).[17,20]

In the present study, we used the cutoff values for AFP (20 ng/ml) and DCP (40 mAU/ml) proposed by previous studies and used most commonly in clinical settings.[2] Considering that much higher AFP values, e.g., 100 ng/ml or 200 ng/ml, have often been proposed as cutoff points, it is noteworthy that the present cutoff value showed better performance than these cutoff values, and even lower cutoff values can be adopted in terms of ROC performance (Table 3, Fig. 1). The cutoff value for DCP in the present study (40 mAU/ml), showing similar sensitivity to that of AFP, was thought to be the lowest among the values proposed until now (40–125 mAU/ml). Again, analysis of the ROC curve revealed that this value can be reduced even further in terms of a trade-off between sensitivity and specificity.

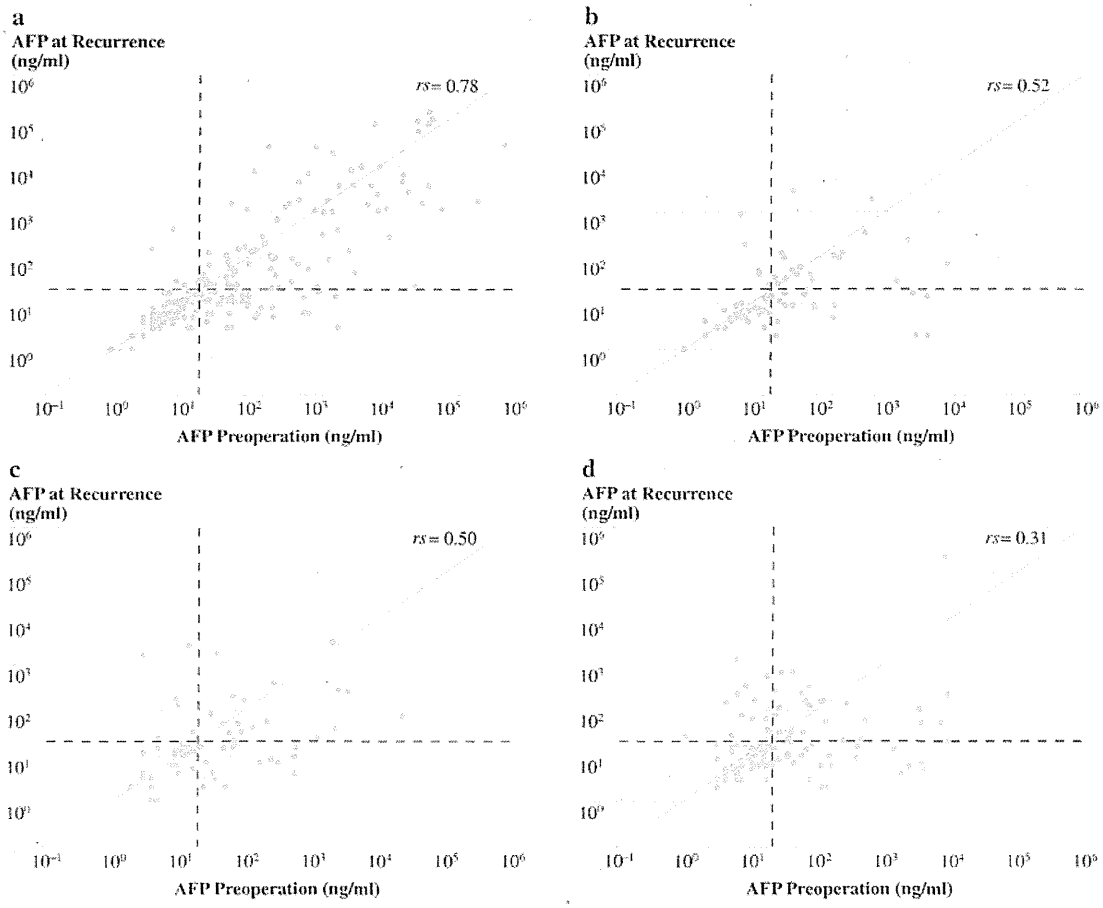

FIG. 3 Correlations between preoperative AFP values and AFP values at recurrence stratified according to period of recurrence: (**a**) recurrence ≤6 months (n = 190), (**b**) recurrence from 7 to 12 months (n = 70), (**c**) recurrence from 13 to 24 months (n = 70), and (**d**) recurrence >2 years (n = 114). The dotted lines represent 20 ng/ml

In addition, DCP is a superior marker for monitoring response to therapy, that is, it was confirmed that positive DCP status converted to negative status in 99.6% (245/246) of patients at 6 months post surgery in the absence of tumor recurrence; in contrast, conversion from AFP-positive to AFP-negative status was achieved in only 80.3% of the patients (184/229). This high false-positive rate of AFP is thought to reflect the observed elevation in the levels of this marker also in conditions such as acute and/or chronic hepatitis and cirrhosis, which is an inherent drawback of AFP as a HCC-specific tumor marker. Whereas high DCP values have been reported in patients with vitamin K deficiency, such as in cases of obstructive jaundice or cases receiving vitamin K antagonists, e.g., warfarin, these uncommon clinical situations can be easily discriminated in HCC patients. Rather, it must be noted that patients with chronic alcoholism, another high-risk cohort for HCC, often show nonspecific DCP elevation, reportedly in 5–8% of patients. The higher DCP cutoff value adopted by Marrero et al. in their study (125 mAU/mL) may be partially ascribed to the fact that their cohort included a considerable proportion of alcoholic patients (5%).

In the present study, no correlation was found between the levels of AFP and DCP. This observation is consistent with previous reports. These results strongly suggest that these markers are complementary to each other and that, although DCP might be superior to AFP as a single marker, the two should be evaluated in combination in clinical practice.

Although the association of tumor markers with various clinicopathological variables has been evaluated in many studies, the majority of these works assessed the associations solely with variables of interest and/or exclusively for AFP or DCP. Bearing this in mind, we investigated these associations in a comprehensive manner. While serum DCP values increased with increasing tumor size, no similar association was found for AFP (Table 2). This result is consistent with the results of previous

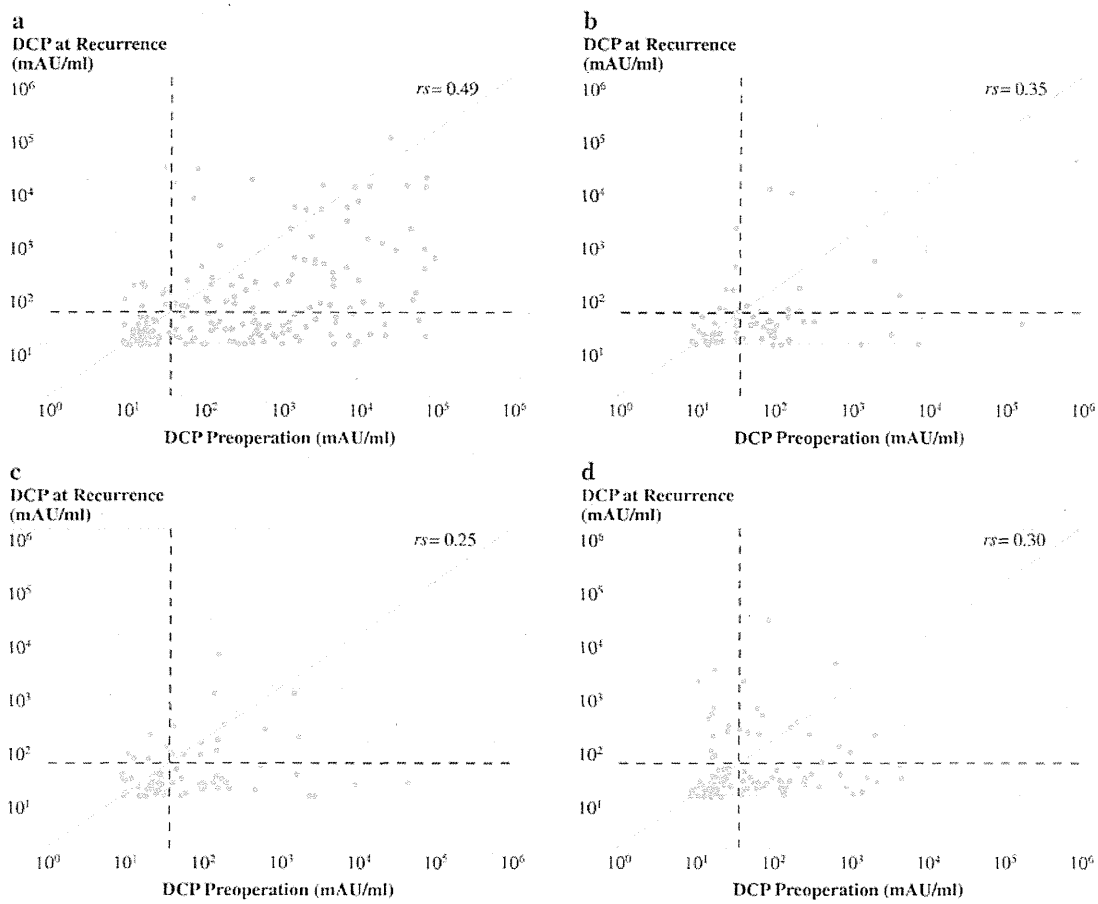

FIG. 4 Correlations between preoperative DCP values and DCP values at recurrence stratified according to period of recurrence: (**a**) recurrence ≤6 months (n = 190), (**b**) recurrence from 7 to 12 months (n = 70), (**c**) recurrence from 13 to 24 months (n = 70), and (**d**) recurrence >2 years (n = 114). The dotted lines represent 40 mAU/ml

studies. These findings suggest that the interindividual variations in the capacity of the tumor cells to synthesize AFP far exceed the elevation in the marker values with increasing tumor cell number.

While serum AFP levels tended to increase with increasing tumor number, this association was not observed for plasma DCP (Table). This finding is consistent with those of Kasahara et al. and Carr et al., who found a significant relationship between AFP and tumor number. Considering that tumor number is thought to be a variable representing the degree of carcinogenicity in the background liver, the finding of the association for AFP but not for DCP is most probably explained by the elevation of AFP with advancing severity of background liver disease.

In the present cohort (n = 714), both increased AFP and DCP values were related to presence of indices of tumor invasiveness, such as vascular invasion, and intrahepatic metastases. To date, several studies with 72–161 patients have investigated the association of AFP and/or DCP with these indices, three of which assessed these pathological variables on surgically resected specimens. A closer and/or specific relationship between these indices and DCP has been reported. Thus, the results of the present and former studies were partially contradictory. In our study, the AFP and DCP values were associated to a similar extent with the tumor cell differentiation grade (Table). Again, this observation is partially contradictory to the results of previous studies with 56–354 patients that claimed a specific close association with AFP or DCP. The results of the present large cohort strongly suggests that both increased levels of AFP and DCP indicate the overall presence of pathological indices representing tumor invasiveness and/or increased malignant potential; however, they do not necessarily signify the presence of any specific entity.

Elevated preoperative AFP and/or DCP levels were correlated with early postoperative recurrence (≤6 months), and recurrence in the early phase was characterized by high serum levels of tumor markers. These results can most reasonably be interpreted as follows: high tumor marker levels signify an increased malignant

potential of the tumor, and the majority of recurrences in the early phase represent recurrence by metastasis, while the later phase of recurrences most often represent secondary de novo tumors whose malignant potential has not yet increased during the process of multistep carcinogenesis. This contention is further supported by the observed association of elevated tumor marker levels with a higher frequency of extrahepatic recurrence.

Two different underlying mechanisms are thought to contribute to postoperative HCC recurrence. In theory, recurrence by metastasis takes place in the early period after surgery, whereas recurrence in the late phase largely represents a new primary lesion. Likewise, it can be hypothesized that (1) metastatic recurrence exhibits similar tumor characteristics to the primary lesion, while de novo lesions are independent of the primary tumors in terms of the marker expression profile, and (2) tumor marker levels in recurrent tumors in the early phase show a close relationship with those before hepatectomy, while this relationship becomes obscure in recurrent tumors in the late phase. Chronological alterations in the correlation coefficients (Figs. and) support this hypothesis. Moreover, this correlation was stronger for AFP than for DCP across all the study groups. This observation suggests that the increased AFP values both before hepatectomy and at the time of recurrence are at least partially accounted for by the background liver diseases.

A limitation of this investigation is that all of the study patients underwent curative liver resections. They would therefore be supposed to exhibit relatively well-preserved liver function, despite the presence of cirrhosis, from the viewpoint of screening. Likewise, they would be expected to have relatively early stage of HCC as compared with patients undergoing transcatheter arterial embolization, from the standpoint of prediction of response to therapies.

In conclusion, although DCP might be more accurate than AFP for the differentiation of HCC from nonmalignant chronic liver disease, the two markers are complementary to each other. The levels of both markers increased with tumor growth, but no specific association of either with any specific pathological entities was noted. The observed relationship between the preoperative marker values and the values measured at the time of recurrence may serve as a basis for predicting the pattern of recurrence of HCC, i.e., recurrence by metastasis or de novo secondary lesions.

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CLINICAL–LIVER, PANCREAS, AND BILIARY TRACT

Neither Multiple Tumors Nor Portal Hypertension Are Surgical Contraindications for Hepatocellular Carcinoma

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Background & Aims: The surgical indications for multiple hepatocellular carcinomas (HCCs) and for HCC with portal hypertension (PHT) remain controversial. ***Methods:*** We reviewed 434 patients who had undergone an initial resection for HCC and divided them into a multiple (n = 126) or single (n = 308) group according to the number of tumors. We also classified 386 of the patients into a PHT group (n = 136) and a no-PHT (n = 250) group according to whether they had PHT (defined by the presence of esophageal varices or a platelet count of $<100{,}000/\mu L$ in association with splenomegaly). ***Results:*** Among Child–Pugh class A patients, the overall survival rates in the multiple group were 58% at 5 years, and 56% in the PHT group, which were lower than those in the single group (68%, $P = .035$) and the no-PHT group (71%, $P = .008$). Among Child–Pugh class B patients with multiple HCCs, the 5-year overall survival rate was 19%. Multivariate analyses revealed that the presence of multiple tumors was an independent risk factor for postoperative recurrence (relative risk, 1.64; 95% confidence interval, 1.23–2.18; $P = .001$). A second resection resulted in satisfactory overall survival after the diagnosis of recurrence in the multiple (73% at 3 years) or PHT (73%) groups, as well as in the single (79%) or no PHT (81%) groups. ***Conclusions:*** Resection can provide survival benefits even for patients with multiple tumors in a background of Child–Pugh class A cirrhosis, as well as in those with PHT.

Liver resection has been a mainstay of treatment for hepatocellular carcinoma (HCC) in patients with well-preserved liver function. Thanks to remarkable advances in diagnosis, surgical techniques, and perioperative care, liver resection now provides a good survival rate, exceeding 50% at 5 years with a surgical mortality rate of 0.8% in Japan according to the latest nationwide survey.[1] Surgical mortality rates range from 0% to 6.4% at major hepatobiliary centers in other countries.[2–6] However, high recurrence rates between 70% and 100% at 5 years[1,2,4,6–12] remain a major drawback to liver resection. One of the most significant predictors of recurrence is the number of tumors.[8,13–15] Previous studies have shown that the 5-year disease-free survival rates after resection for multiple HCCs range from 0% to 26%, lower than those for a single HCC (31%–46%).[6,8,10,11] The surgical indications for multiple HCCs have not been established.

The degree of liver damage is another significant prognostic factor after resection for HCC. In 1996, Bruix et al[16] reported that liver resection for HCC in patients with portal hypertension (PHT), as defined by a hepatic venous pressure gradient of 10 mm Hg or greater, led to a high incidence (73%) of postoperative liver decompensation with a poor 5-year survival rate of less than 50%. Their results provided supporting evidence for the Barcelona Clinic Liver Cancer staging system proposed in 1999, in which liver resection was contraindicated for patients with PHT.[17] In contrast, in eastern Asia liver functional reserve usually is evaluated by the indocyanine green test before surgery, rather than the presence or absence of PHT.[3,6,18–20] The surgical indications for HCC associated with PHT also remain controversial.

Recently, treatment guidelines for HCC that are based on the Barcelona Clinic Liver Cancer staging system[17] have been proposed in Europe[21] and the United States.[22] These guidelines recommend liver resection only for patients with a single HCC without PHT. Liver transplantation or percutaneous ablation is recommended for a single HCC with PHT and for small multiple HCCs (up to 3 nodules and smaller than 3 cm), and transcatheter arterial chemoembolization is proposed for other types

Abbreviations used in this paper: CT, computed tomography; ICGR15, indocyanine green retention rate at 15 minutes; PHT, portal hypertension.

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of multiple HCCs.[21,22] One reason for the narrow indications for resection is the poor long-term outcomes in patients with multiple HCCs[8,13–15] and/or PHT.[14,16] However, recent advances in liver surgery have rapidly improved outcomes, especially in eastern Asia. The aim of this study was to assess the therapeutic value of liver resection for multiple HCCs and for HCC with PHT and to re-evaluate the current treatment algorithms for HCC, such as the Barcelona Clinic Liver Cancer staging system, which were constructed on the basis of data obtained mainly in Western countries.

Materials and Methods

The study was undertaken in accordance with the Declaration of Helsinki.

Patients

The base population consisted of 455 consecutive patients who had undergone an initial curative liver resection for HCC without extrahepatic metastasis at Tokyo University Hospital between November 1994 and December 2004. We excluded 21 patients in whom a malignancy other than HCC had been diagnosed within a 5-year period before liver resection. The remaining 434 patients were enrolled in the present study. First, we classified them into multiple (n = 126) and single (n = 308) groups according to the number of HCCs that were present, which was determined according to the pathologic findings. We regarded a tumor with a surrounding co-nodule(s) as a single tumor only when the co-nodule(s) was attached to the main tumor.

Second, we divided 386 of the earlier-described 434 patients into a PHT group (n = 136) and a no-PHT (n = 250) group according to the presence or absence of PHT. Forty-eight patients were excluded because no records of preoperative upper-gastrointestinal endoscopy were available. PHT was defined according to the criteria proposed by the Barcelona group for patients in whom the hepatic venous pressure gradient was not measured (ie, the presence of esophageal varices and/or a platelet count of $<100{,}000/\mu L$ in association with splenomegaly).[17] Splenomegaly was diagnosed by preoperative computed tomography (CT), according to one of the widely used criteria for splenomegaly (ie, a spleen length exceeding 10 cm on CT).[23] The PHT group consisted of 57 patients with a platelet count of less than $100{,}000/\mu L$ in association with splenomegaly, 37 patients with esophageal varices, and 42 patients with both conditions.

The study group comprised 364 patients with cirrhosis of Child–Pugh class A and 70 with cirrhosis of Child–Pugh class B (68 patients with a score of 7 and 2 with a score of 8).[24] Among Child–Pugh class B patients, 2 had Gilbert syndrome and 1 had obstructive jaundice caused by tumor thrombus in the bile duct. None of the other patients had encephalopathy, uncontrollable ascites, or jaundice (serum total bilirubin level, ≧2.0 mg/dL). Table 1 shows the background characteristics in each group. Liver function was worse in the multiple group than in

Table 1. Background Characteristics

Variable	Multiple (n = 126)	Single (n = 308)	*P*	PHT (n = 136)	No PHT (n = 250)	*P*
Median age, y (range)	65 (32–90)	65 (13–85)	.371	65 (16–90)	66 (13–85)	.417
Sex						
Male	97 (77%)	239 (78%)	.900	88 (65%)	209 (84%)	<.001
Female	29 (23%)	69 (22%)		48 (35%)	41 (16%)	
Platelet count, $\times 10^3/\mu L$ (range)	124 (23–444)	147 (33–486)	.001	83 (23–237)	169 (100–486)	<.001
Median albumin level, g/dL (range)	3.6 (2.7–4.7)	3.7 (2.7–4.8)	.072	3.6 (2.7–4.5)	3.8 (2.7–4.8)	<.001
Total median bilirubin level, mg/dL (range)	0.8 (0.3–1.7)	0.7 (0.2–5.0)	.308	0.8 (0.3–1.9)	0.7 (0.2–5.0)	<.001
Median prothrombin rate, % (range)	74.8 (48.7–100)	78.8 (48.4–100)	.022	72.4 (50.5–100)	79.6 (48.7–100)	<.001
Median ICGR15, % (range)	17.4 (5.3–45.0)	13.7 (2.2–48.0)	<.001	20.0 (5.0–48.0)	13.1 (2.2–45.0)	<.001
Child–Pugh class						
A	105 (83%)	259 (84%)	.886	98 (72%)	224 (90%)	<.001
B	21 (17%)	49 (16%)		38 (28%)	26 (10%)	
Esophageal varices[a]						
Yes	31 (27%)	48 (18%)	.053	79 (60%)	0 (0%)	<.001
No	83 (73%)	219 (82%)		52 (40%)	250 (100%)	
Hepatitis B virus surface antigen						
Positive	12 (10%)	74 (24%)	.001	16 (12%)	59 (24%)	.005
Negative	114 (90%)	234 (76%)		120 (88%)	191 (76%)	
Hepatitis C virus antibody						
Positive	93 (74%)	187 (61%)	.011	104 (76%)	147 (59%)	.001
Negative	33 (26%)	121 (39%)		32 (24%)	103 (41%)	
Background liver						
Cirrhosis	103 (82%)	228 (74%)	.106	123 (90%)	170 (68%)	<.001
Noncirrhosis	23 (18%)	80 (26%)		13 (10%)	80 (32%)	

[a]Evaluated using gastroesophageal fiberscopy in 386 patients.

Table 2. Cancer-Related Factors

Variable	Multiple (n = 126)	Single (n = 308)	*P*	PHT (n = 136)	No PHT (n = 250)	*P*
Tumor number						
Single	—	308 (100%)	—	83 (61%)	189 (76%)	.004
Multiple	—	—		53 (39%)	61 (24%)	
2	75 (60%)	—		—	—	
3	29 (23%)	—		—	—	
≥4[a]	22 (17%)	—		—	—	
Median main tumor size, *mm (range)*	35 (11–140)	35 (8–160)	.509	28 (12–90)	40 (8–160)	<.001
Microscopic vascular invasion						
Yes	34 (27%)	68 (22%)	.318	27 (20%)	59 (24%)	.444
No	92 (73%)	240 (78%)		109 (80%)	191 (76%)	
Cancer cell differentiation						
Well	19 (15%)	42 (14%)	.761	25 (18%)	32 (13%)	.176
Moderate or poor	107 (85%)	266 (86%)		111 (82%)	218 (87%)	
Median α-fetoprotein level, ng/mL	57 (2–400,000)	19 (1–436,000)	.039	33 (1–45,934)	19 (1–436,000)	.126
Des-γ-carboxy prothrombin						
Positive	77 (61%)	163 (53%)	.137	51 (38%)	158 (63%)	<.001
Negative	49 (39%)	145 (47%)		85 (62%)	92 (37%)	

[a]Tumor number was 4 (n = 14), 5 (n = 2), 6 (n = 4), and 9 (n = 2).

the single group and also was worse in the PHT group than in the no-PHT group. Hepatitis C virus infection was more common in the multiple group than in the single group and also was more common in the PHT group than in the no-PHT group. Cancer-related characteristics are shown in Table 2.

Indications for Liver Resection

The indications for liver resection and surgical procedures were determined according to a decision tree based on the presence or absence of uncontrolled ascites, the serum bilirubin level, and the indocyanine green retention rate at 15 minutes (ICGR15),[18,25] irrespective of the presence or absence of PHT. Briefly, if the serum bilirubin level was normal, our criteria permitted right hepatectomy or trisectoriectomy when the ICGR15 was less than 10%, left hepatectomy or sectoriectomy when the ICGR15 was less than 20%, subsegmentectomy or Couinaud's segmentectomy when the ICGR15 was less than 30%, limited resection when the ICGR15 was less than 40%, and enucleation when the ICGR15 was 40% or greater.

Preoperative Treatment of PHT

For patients with a platelet count of less than 50,000/μL, we additionally performed splenectomy before (n = 3) or concurrently with (n = 6) liver resection to reduce the risk of hemorrhagic complications. If an upper-gastrointestinal endoscopic examination revealed either moderately enlarged beady varices (grade F2)[26] with or without a red color sign or markedly enlarged nodular or tumor-shaped varices (F3), we performed endoscopic treatments preoperatively such as variceal band ligation (n = 14) or sclerotherapy (n = 2) to avoid variceal rupture.[27] For patients with gastric varices and for those who had esophageal varices with a low platelet count (<50,000/μL), the surgery described by Hassab[28] (gastroesophageal devascularization and splenectomy) was performed before (n = 3) or concurrently with liver resection (n = 5).[27]

Diagnosis of HCC

Before surgery, all patients underwent abdominal ultrasonography. Enhanced CT, hepatic angiography with the injection of iodized oil (Lipiodol Ultrafluid; Andre Guerbet, Aulnay Soubois, France), and Lipiodol CT were performed in 416 (96%), 413 (95%), and 428 (99%) of the 434 patients, respectively.[29–31] Patients who could not undergo enhanced CT were evaluated by gadolinium-enhanced magnetic resonance imaging. In principle, resection was indicated for lesions suspected to be HCC when both early hyperenhancement and delayed hypoenhancement were observed on images obtained with any modality.[29,30] During surgery, the liver was evaluated by visual inspection, manual palpation, and intraoperative ultrasonography.[18,32] Newly detected HCC was resected whenever possible.[18,25,32,33]

Preoperative imaging studies accurately diagnosed the tumor number, which was confirmed by postoperative pathologic examination, in 360 (83%) of the 434 patients. In the remaining patients, the tumor number was underestimated (n = 57; 13%) or overestimated (n = 17; 4%) before surgery. Among 126 patients in the multiple group, a single tumor was diagnosed preoperatively in 37 (29%). In these latter patients, postoperative examinations confirmed 1 (n = 22), 2 (n = 12), or 3 (n = 3) additional tumor(s), ranging in diameter from 3 to 22 mm (median, 8 mm).

Surgery

Anatomic resections[32] of a subsegment, Couinaud's segment, sector, or hemiliver were the preferred surgical

Table 3. Surgical Outcomes

Variable	Multiple (n = 126)	Single (n = 308)	*P*	PHT (n = 136)	No PHT (n = 250)	*P*
Extent of resection(s)						
<1 sector	106 (84%)	244 (79%)	.285	133 (98%)	186 (74%)	<.001
≥1 sector	20 (16%)	64 (21%)		3 (2%)	64 (26%)	
Number of resection(s)						
Single resection	40 (32%)	307 (99.7%)	<.001	91 (67%)	216 (86%)	<.001
≥2 resections	86 (68%)	1 (0.3%)[a]		45 (33%)	34 (14%)	
Anatomic resection						
Yes	45 (36%)	219 (71%)	<.001	53 (39%)	170 (68%)	<.001
No	81 (64%)	89 (28%)		83 (61%)	80 (32%)	
Surgical time, min (range)[a]	375 (35–975)	330 (80–810)	<.001	325 (80–725)	360 (35–975)	.165
Blood loss, mL (range)	753 (100–6700)	610 (15–4830)	.002	620 (20–4830)	640 (15–6700)	.629
Red blood cell transfusion[a]						
Yes	7 (6%)	15 (5%)	.811	6 (4%)	10 (4%)	<.999
No	119 (94%)	293 (95%)		130 (96%)	240 (96%)	
Surgical margin, mm						
0	67 (53%)	77 (25%)	<.001	54 (40%)	77 (31%)	.091
>0	59 (47%)	231 (75%)		82 (60%)	173 (69%)	
Median maximum total bilirubin level after surgery, mg/dL (range)	1.1 (0.5–5.5)	1.1 (0.4–12.8)	.748	1.2 (0.4–12.8)	1.1 (0.4–3.4)	<.001
Complications[b]						
Yes	19 (15%)	27 (9%)	.060	13 (10%)	30 (12%)	.503
No	107 (85%)	281 (91%)		123 (90%)	220 (88%)	
Median postoperative hospital stay, days (range)	19 (9–88)	17 (7–61)	.001	20 (7–88)	16 (9–61)	.005

[a]Pathologic examination revealed 1 of the 2 independently resected specimens to be a dysplastic nodule.
[b]Complications included bile leakage (n = 22), ascites or pleural effusion (n = 13), intra-abdominal abscess (n = 3), cerebral infarction (n = 2), postoperative bleeding, cholangitis, acute renal failure, lung edema, colitis, and rupture of esophageal varices (n = 1).

procedures, if such a resection was permitted according to the earlier-described criteria. For multiple HCCs, anatomic resection was defined as the complete removal of all tumor-bearing subsegments.

Table 3 shows the surgical outcomes. Two thirds of the patients with multiple tumors underwent 2 or more concomitant liver resections. Patients in the PHT group tended to undergo smaller and multiple liver resection(s) as compared with those in the no-PHT group. The feasibility of anatomic resection was significantly lower in the multiple group and the PHT group than in the single group and the no-PHT group, respectively. Resections in the multiple group required longer surgical times and were associated with a larger blood loss than those in the single group. The percentage of tumors with a 0-mm surgical margin was higher in the multiple group, although none of the tumors were incised during the resections. The maximum postoperative total bilirubin values were higher in the PHT group than in the no-PHT group. Surgical morbidity did not differ between the groups. All the patients recovered well, except for 1 patient with a single HCC and PHT (grade F3 esophageal varices and a platelet count of 85,000/μL) who died from liver failure 20 days after resection after the rupture of the varices on postoperative day 4.

Follow-Up Evaluation

The blood tumor markers (α-fetoprotein and plasma des-γ-carboxy prothrombin) and ultrasonography findings were examined every 3 months after the patients were discharged, and enhanced CT findings were examined every 6 months. Postoperative antiviral treatment usually was not administered.

Recurrence was defined as the appearance of a new lesion with the radiologic features of HCC. The recurrence types and treatments given were obtained from clinical records.

Treatments for Recurrence

For intrahepatic recurrence, a second liver resection was the treatment of choice if the resection was feasible on the basis of liver function, evaluated according to the same criteria as those used at the time of initial resection.[18,25,34] Patients with resectable extrahepatic invasion or distant metastases also were candidates for resection.[34] If a second resection was contraindicated because of poor liver function and/or unfavorable characteristics of recurrence, transcatheter arterial chemoembolization was performed repeatedly.

Statistical Analyses

The survival curves and cumulative recurrence rates were estimated with the Kaplan–Meier method and were compared using the log-rank test. A multivariate analysis was performed using the Cox proportional-hazards model and the backward-elimination procedure. A *P* value of less than .20 was set as the cut-off value for the elimination. The presence or absence of PHT, tumor

number (multiple vs single), and the following 14 other variables, considered potential confounders, were examined: age (≥ vs <65 y), sex, total bilirubin level (≥ vs < 1 mg/dL), ICGR15 (≥ vs < 20%), Child–Pugh class (A vs B), positivity for hepatitis C virus antibody, background liver status (cirrhosis vs noncirrhosis), main tumor size (≥ vs < 50 mm), microscopic vascular invasion (negative vs positive), cancer cell differentiation (well vs moderately or poor), serum α-fetoprotein level (≥ vs <400 ng/mL), plasma des-γ-carboxy prothrombin level (positive vs negative), intraoperative red blood cell transfusion (yes vs no), and surgical margin (= vs > 0 mm). Continuous data are expressed as the medians (range), unless otherwise stated. Categoric and continuous data were compared between groups using the Fisher exact test and the Wilcoxon rank-sum test, respectively. Significance was defined as a P value of less than .05. Calculations were performed using SPSS software (version 11.51J; SPSS Inc., Chicago, IL).

Results

The median follow-up period after surgery was 46 months (range, 1–137 mo). Long-term overall survival was significantly poorer in the multiple group than in the single group: the 3-year/5-year overall survival rates were, respectively, 72%/58% in the multiple group and 81%/68% in the single group among patients with Child–Pugh class A cirrhosis (P = .035) and 33%/19% in the multiple group and 72%/45% in the single group among those with Child–Pugh class B cirrhosis (P = .013; Figure 1*A*). The 3-year/5-year cumulative recurrence rates, were respectively, 73%/75% in the multiple group and 47%/60% in the single group among patients with Child–Pugh class A cirrhosis (P < .001) and 87%/100% in the multiple group and 73%/73% in the single group among patients with Child–Pugh class B cirrhosis (P = .002; Figure 1*B*).

Long-term overall survival was poorer in the PHT group than in the no-PHT group. Among patients with Child–Pugh class A cirrhosis, the 3-year/5-year overall survival rates were, respectively, 71%/56% in the PHT group and 81%/71% in the no-PHT group (P = .008), whereas the 3-year/5-year cumulative recurrence rates were, respectively, 63%/75% in the PHT group and 50%/58% in the no-PHT group (P = .008). Among patients with Child–Pugh class B cirrhosis, long-term outcomes did not differ between the groups: the 3-year/5-year overall survival rates were, respectively, 59%/41% in the PHT group and 62%/31% in the no-PHT group, (P = .681), whereas the 3-year/5-year cumulative recurrence rates were, respectively, 84%/88% in the PHT group and 63%/73% in the no-PHT group (P = .356; Figure 1*C* and *D*).

Table 4 shows the results of the multivariate analyses. The presence of multiple tumors was not a significant predictor of overall survival but independently increased the risk of recurrence (relative risk, 1.64; 95% confidence interval, 1.23–2.18; P = .001). PHT had no prognostic value with regard to the overall survival rate or the cumulative recurrence rate. Child–Pugh class B was a strong predictor of a poor overall survival after resection.

Among patients with recurrence, the proportion of those with Child–Pugh class B cirrhosis at the detection

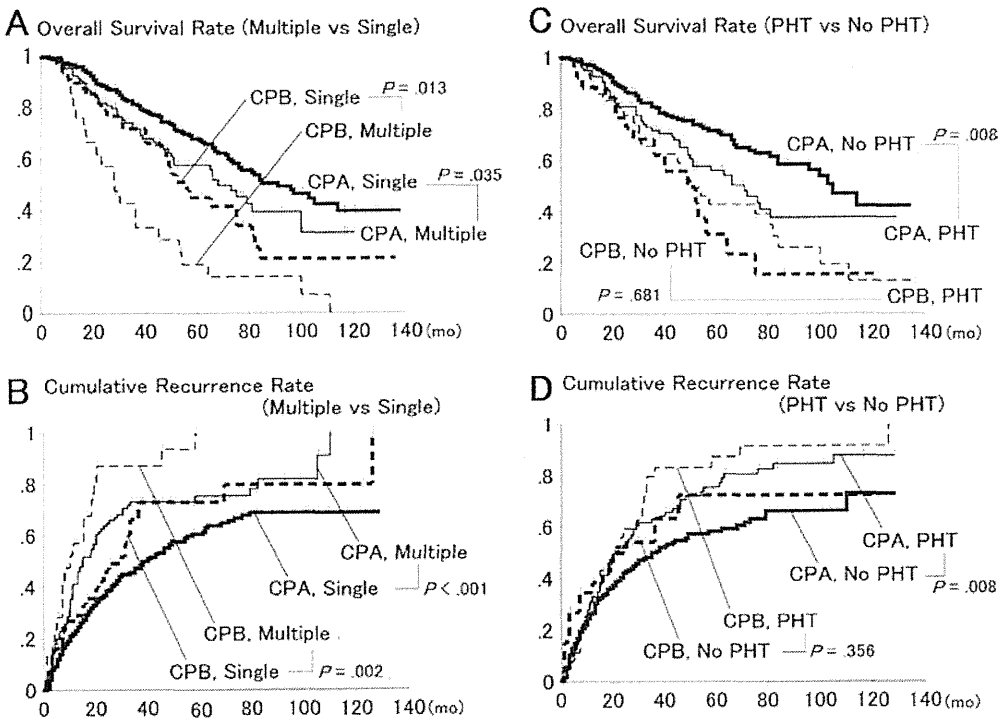

Figure 1. (*A*) Overall survival curves and (*B*) cumulative recurrence rates after liver resection in patients with a single tumor and in those with multiple tumors, and (*C*) overall survival curves and (*D*) recurrence rates in patients with PHT and in those without PHT. Patients were stratified according to their Child–Pugh class. CPA, Child–Pugh class A; CPB, Child–Pugh class B.

Table 4. Multivariate Analyses

Variable	Relative risk	95% confidence interval	*P*
Overall survival			
Child–Pugh class B	1.96	1.34–2.86	.001[a]
Microscopic vascular invasion	1.72	1.20–2.46	.003[a]
Hepatitis C virus–antibody positive	1.60	1.11–2.32	.013[a]
Des-γ-carboxy prothrombin, positive	1.44	1.02–2.04	.041[a]
Portal hypertension	1.29	0.91–1.84	.153
Multiple tumor number	1.21	0.86–1.70	.285
Cumulative recurrence rate			
Multiple tumor number	1.64	1.23–2.18	.001[a]
Child–Pugh class B	1.47	1.05–2.08	.027[a]
Microscopic vascular invasion	1.41	1.03–1.91	.030[a]
Portal hypertension	1.19	0.91–1.56	.213

[a]Statistically significant.

of recurrence was higher in the multiple group than in the single group; the proportion of such patients also was higher in the PHT group than in the no-PHT group (Table 5). The sites and the sizes of the recurrent tumors were similar in the multiple and single groups, as well as in the PHT and no-PHT groups. The proportion of patients with recurrence in whom a second liver resection was indicated was lower in the multiple group than in the single group (22% vs 41%; $P = .002$).

Overall survival after the diagnosis of recurrence was better among the patients with recurrence who underwent a second resection as compared with those who did not in the multiple group (3-year survival rates, 73% vs 40%; $P = .023$) and the PHT group (73% vs 34%; $P = .004$), as well as in the single group (79% vs 31%; $P < .001$) and the no-PHT group (81% vs 37%; $P < .001$; Figure 2*A* and *B*).

During the follow-up period, 162 patients (84%) died of HCC recurrence, 8 (4%) died of liver failure without evidence of recurrence, and 23 (12%) died of other diseases, including pneumonia (n = 9), ischemic heart disease (n = 7), sepsis associated with diabetic gangrene (n = 2), acute renal failure (n = 1), cerebral bleeding (n = 1), pulmonary embolism (n = 1), meningitis (n = 1), and pancreatic cancer (n = 1).

Discussion

In our series, liver resection was associated with a 5-year overall survival rate of nearly 60% in patients with HCC who had multiple tumors or PHT (or both), if their liver function remained within the range of Child–Pugh class A. The overall survival of these patients exceeded the currently accepted limit for curative treatment of HCC (a 5-year overall survival of 50%)[22,35] and compared favorably with previous results after resection (24%–60% for patients with multiple HCCs,[1,4,6,8–11] and 17%–50% for those with PHT[12,14,36]; Table 6).

One of the reasons why liver resection has been avoided in patients with multiple HCCs is the high frequency of recurrence, estimated to exceed 70% at 5 years.[6,8,10,11] In fact, irrespective of liver function (Child–Pugh class A or B), recurrence rates after resection for multiple HCCs were higher than those for a single HCC in this study (Figure 1*B*), consistent with previous findings.[6,8,10,11] Multivariate analysis also identified tumor multiplicity as an independent predictor of postoperative recurrence. These results were as expected because multiplicity suggests a more advanced stage of cancer than a single tumor.

In our study, overall survival after resection for multiple HCCs was worse than that after resection for a single HCC (Figure 1*A*); this finding also is reasonable. How-

Table 5. Characteristics and Treatments for Recurrences

Variable	Multiple (n = 126)	Single (n = 308)	*P*	PHT (n = 136)	No PHT (n = 250)	*P*
No recurrence	26 (21%)	117 (38%)	.001	27 (20%)	104 (42%)	<.001
Recurrence	100 (79%)	191 (62%)		109 (80%)	146 (58%)	
Liver function at time of recurrence						
Child–Pugh class A	57 (57%)	136 (71%)	.019	54 (50%)	112 (77%)	<.001
Child–Pugh class B	43 (43%)	55 (29%)		55 (50%)	34 (23%)	
Site of recurrence						
Extrahepatic[a]	5 (5%)	19 (10%)	.181	5 (5%)	16 (11%)	.105
Intrahepatic	95 (95%)	172 (90%)		104 (95%)	130 (89%)	
Number of intrahepatic recurrences						
Single	36 (38%)	71 (41%)	.748	45 (43%)	51 (39%)	.593
Multiple	59 (62%)	101 (59%)		59 (57%)	79 (61%)	
Recurrent tumor size, mm	15 (5–30)	15 (8–35)	.635	15 (8–35)	15 (5–35)	.170
Treatments for recurrence						
Second liver resection	22 (22%)	78 (41%)	.002	35 (32%)	52 (36%)	.595
Other treatments	88 (78%)	113 (59%)		74 (68%)	94 (64%)	
Transarterial chemoembolization	64 (73%)	76 (67%)		50 (68%)	65 (69%)	
Percutaneous treatments	12 (14%)	14 (12%)		12 (16%)	12 (13%)	
Living donor liver transplantation	1 (1%)	0 (0%)		1 (1%)	0 (0%)	

[a]Including 15 patients with both intrahepatic and extrahepatic recurrences.

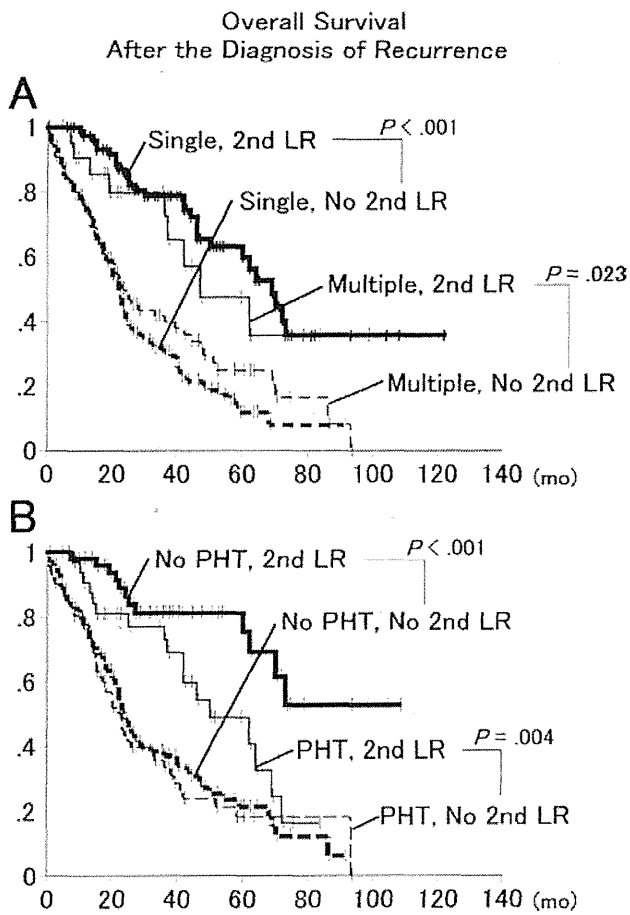

Figure 2. Overall survival curves after the diagnosis of recurrence between patients who underwent a second liver resection (2nd LR) and those who did not (No 2nd LR), stratified according to the (*A*) tumor number and the (*B*) presence or absence of portal hypertension at the time of the primary surgery.

ever, among patients with better liver function of Child-Pugh class A, the absolute survival rate at 5 years was as high as 58%, one of the best results among previous studies (Table 6).[1,4,6,8-11] Why were satisfactory results obtained, despite the high recurrence rate of more than 70% at 5 years? One reason might be linked to our strategy for managing recurrence. We have actively performed repeat resections for recurrent HCCs and obtained good results.[3,4] In the present study, a second resection resulted in satisfactory overall survival after the diagnosis of recurrence among patients who had had single or multiple HCCs at the time of their primary surgery (79% and 73% at 3 years, respectively, Figure 2*A*).

One of the problems in the present study was that a second resection for the treatment of recurrence was less feasible among patients who had undergone primary surgery for multiple HCCs (22%) than for those who underwent primary surgery for a single HCC (41%). Because the selection criteria for a second resection were the same as those used for the primary resection, the lower feasibility of a second resection might have been caused by a worsening of tumor- or liver-function-related factors. The characteristics of recurrent HCC did not differ between the single and multiple groups, suggesting that the poorer liver function at the time of recurrence was the main obstacle to a second resection in the multiple group. Indeed, survival after primary surgery was poor in patients with Child-Pugh class B cirrhosis who had multiple HCCs (5-year overall survival, <20%). Thus, patients with multiple HCCs and Child-Pugh class B cirrhosis are not good candidates for liver resection.

Table 6. Review of Outcomes After Liver Resection

Reference	n	Overall survival 1 y	Overall survival 5 y	Disease-free survival 1 y	Disease-free survival 5 y
Tumor number					
Fong et al,[4] 1999					
Single HCC	113	81%	35%	ND	ND
Multiple HCCs	42	76%	48%	ND	ND
Poon et al,[8] 2002[a]					
Single HCC	115	91%	72%	76%	40%
2 or 3 HCCs, <30 mm	20	86%	60%	57%	0%
Vauthey et al,[9] 2002					
Single HCC	370	ND	45%	ND	ND
Multiple HCCs	180	ND	24%	ND	ND
Ercolani et al,[10] 2003					
Single HCC	200	ND	ND	80%	31%
Multiple HCCs	24	ND	ND	55%	0%
Ikai et al,[1] 2007					
Single HCC	19,046	91%	59%	ND	ND
2 HCCs	4011	86%	46%	ND	ND
≥3 HCCs	3174	75%	30%	ND	ND
Wu et al,[6] 2005					
Single HCC	337	ND	62%	ND	46%
Multiple HCCs	82	ND	26%	ND	26%
Portolani et al,[11] 2006					
Single HCC	175	ND	47%	ND	64%[b]
Multiple HCCs	38	ND	29%	ND	80%[b]
Current study[a]					
Single HCC	308	97%	68%	23%[b]	60%[b]
Multiple HCCs	126	96%	58%	41%[b]	75%[b]
PHT					
Llovet et al,[14] 1999					
No PHT and normal bilirubin level	35	91%	74%	ND	ND
PHT and normal bilirubin level	15	93%	50%	ND	ND
PHT and abnormal bilirubin level	27	74%	25%	ND	ND
Cillo et al,[26] 2004					
No PHT	23	87%	74%	ND	ND
PHT	23	69%	17%	ND	ND
Capussotti et al,[12] 2006					
No PHT	99	ND	40%	ND	38%
PHT	118	ND	29%	ND	30%
Current study[a]					
No PHT	250	97%	71%	27%[b]	58%[b]
PHT	136	93%	56%	33%[b]	75%[b]

ND, no data.
[a]Child-Pugh class A patients.
[b]Cumulative recurrence rate.

Our results also indicate that liver resection can be performed safely even in the presence of PHT. The potential risks of resection in patients with PHT are perioperative variceal rupture and hemostatic disorders caused by thrombocytopenia. To avoid these crucial complications, we perform preoperative endoscopic treatments and/or a splenectomy with or without devascularization of the abdominal esophagus and the upper part of the stomach.[27] Another risk factor is postoperative liver failure because patients with PHT tend to have poorer liver function than those without PHT, as observed in our series. To ensure the safety as well as radicality of resection in patients with PHT, we have precisely evaluated liver function on the basis of the ICGR15 value, which reflects uptake function of the liver as well as liver blood flow,[19] to determine the range of liver volume that can be resected safely.[18,19,25] By following this strategy, we were able to avoid PHT-related complications and postoperative liver failure in all but one of our patients. Anatomic resection was indicated in about 40% of the patients with PHT.

In patients with PHT, the high incidence of recurrence owing to a second episode of primary carcinogenesis in the injured liver is also an important problem. In this study, the 5-year cumulative recurrence rate was very high (around 80%) in patients with PHT. The percentage of recurrent lesions resulting from second episodes of primary carcinogenesis and the percentage of those resulting from intrahepatic metastasis are difficult to estimate. Regardless of the pathway of recurrence, however, patients with PHT could receive effective treatments for recurrence, including a second resection with satisfactory overall survival (Figure 2*B*), transcatheter arterial chemoembolization, and percutaneous treatment. The ability to perform these treatments for recurrence did not differ between patients with PHT and those without PHT at the time of primary surgery (Table 5). Thus, we believe that performing the most effective treatment for primary HCC may improve survival, even among patients with PHT. Our aggressive strategy for treating patients with HCC and PHT can be justified by the good 5-year overall survival rate of 56% for patients with Child–Pugh class A cirrhosis, albeit this rate was significantly lower than that in patients without portal hypertension.

Our results suggest 2 major limitations of the treatment guidelines for HCC that are based on the Barcelona Clinic Liver Cancer staging system[17] used in Europe[21] and the United States.[22] First, these guidelines do not recommend liver resection for patients with PHT. Indeed, liver failure and the rupture of varices, which are not related directly to HCC, are 2 of the major causes of mortality in patients with PHT. However, recent advances in perioperative management for patients with cirrhosis and a restrictive liver resection policy[18] have reduced the number of cirrhosis-related deaths, and most of the deaths (84%) in our series were associated with the recurrence of HCC. At present, the benefits of resection in patients with HCC and PHT may thus outweigh the risks of cirrhosis-related mortality after resection.

The second limitation is that the current guidelines recommend only liver transplantation as surgical treatment for patients with multiple HCCs.[17,21,22] Liver transplantation is an ideal treatment for HCC meeting the criteria of Bismuth et al[37] or the Milan criteria[38] because this procedure can replace the precancerous injured liver. Unfortunately, graft shortages are an acute problem worldwide.[39,40] Given the low availability of suitable grafts, the indications of liver resection should be expanded to include multiple HCCs as the second best treatment.[41]

One of the major drawbacks of the present study was the lack of a control group. However, our 5-year overall survival rate of nearly 60% is satisfactory and acceptable, justifying the surgical indications for HCC with multiple tumors or PHT if the liver function remains within Child–Pugh class A. If the safety of liver resections and the outcomes of patients with HCC and cirrhosis have been improved remarkably by recent advances in perioperative management and surgical techniques, the indications for liver resection can now be extended accordingly.

In conclusion, liver resection can provide a survival benefit for patients with multiple HCCs associated with Child–Pugh class A cirrhosis. Resection for HCC also may be indicated for patients with PHT.

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