

Microsatellite Distribution and Indication for Locoregional Therapy in Small Hepatocellular Carcinoma

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BACKGROUND. Intrahepatic disease recurrence is observed frequently after locoregional therapies for patients with hepatocellular carcinoma (HCC). However, the indication for locoregional therapy is still unclear. To clarify the indication for locoregional therapy for small HCC tumors, the authors measured the distance of microsatellites from the main tumor and analyzed the relation between this distance and clinicopathologic factors.

METHODS. The authors retrospectively analyzed 100 patients with small HCC tumors (≤ 5 cm in dimension) treated by curative hepatectomy. A microsatellite was defined as invasion into the portal vein or intrahepatic metastasis, and the distance from the main tumor to the most distant microsatellite was determined under light microscopy. The current study investigated the relation between microsatellite distance (0 mm if none present, ≤ 5 mm, and > 5 mm) and clinicopathologic factors, as well as overall and disease-free survival rates after hepatectomy.

RESULTS. Of the 100 patients, 46 had microsatellites with a mean distance of 9.9 mm (median, 5.0 mm). Of the clinicopathologic factors investigated, tumor grade and preoperative α -fetoprotein level significantly correlated with the presence of a microsatellite. Tumor size and distance to the microsatellite were significantly correlated. All but 1 tumor associated with a microsatellite distance > 5 mm was a high-grade tumor > 25 mm in greatest dimension. The overall survival rate of patients with a microsatellite distance of > 5 mm was lower than that of patients with a microsatellite distance < 5 mm.

CONCLUSIONS. Locoregional therapy, including limited resection and ablation therapies, was appropriate for patients with low-grade HCC tumors or with tumors < 25 mm in diameter. *Cancer* 2005;103:299–306.

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KEYWORDS: hepatocellular carcinoma, micrometastasis, portal invasion, intrahepatic metastasis, thermal ablation.

Hepatocellular carcinoma (HCC) is one of the most common primary liver carcinomas in the world.¹ HCC arises from diseased liver tissue secondary to hepatitis virus infection. Surgical resection is considered the treatment of choice for patients with HCC, provided that the hepatic functional reserve is adequate. However, the majority of patients with HCC are not candidates for resection because of multifocal tumors or poor hepatic functional reserve. Patients with chronic liver disease related to hepatitis C or B virus infection are at high risk of developing HCC.² Such disease is present in approximately 80% of patients with HCC.¹ With the increasing detection of small HCC tumors in screening programs for high-risk patients, use of minimally invasive locoregional therapies, including percutaneous

ethanol injection (PEI) and thermal ablation (i.e., microwave coagulation therapy [MCT], radiofrequency ablation [RFA], and cryotherapy) for unresectable small HCC tumors, has increased.³

HCC cells spread mainly via the portal system and form intrahepatic satellite lesions,^{4,5} similar to other primary and secondary liver carcinoma cells.^{6,7} Even in early HCC (lesions < 2 cm in dimension), the tumor invades the portal vein in 27% of cases, and intrahepatic metastasis occurs in 10% of cases.⁴ Studies show a clinicopathologic basis for determining surgical margins on the basis of frequency^{8,9} or distance to microsatellite lesions in HCC.^{10,11} The indications for PEI and thermal ablation therapy require further investigation. However, most investigators who have performed such therapy suggest that it is indicated for patients with HCC tumors < 30 mm in dimension and with fewer than 3 tumors.^{3,12-15} These indications have been expanded by the development of new modalities such as MCT and RFA.^{3,16-19}

To clarify the indication for local therapy of HCC, we retrospectively analyzed cases of small HCC tumors and measured the distance of microsatellites from the main HCC tumor under light microscopy. We investigated the correlation between microsatellite distribution and clinicopathologic factors, as well as the prognostic significance of microsatellite distribution in patients with HCC.

MATERIALS AND METHODS

Between September 1983 and December 2002, 269 patients with HCC underwent hepatic resection at the Department of Surgery I, Oita University Faculty of Medicine (Oita, Japan). Of these, 19 (7.1%) patients died of postoperative complications within 30 days. Resection with a curative intent, defined by the Liver Cancer Study Group of Japan as resection resulting in the absence of definite residual tumor at the time of surgery,²⁰ was confirmed by histologic examination in the 250 remaining patients. Resected tumors from the 142 patients were \leq 5 cm in dimension. When a tumor thrombus was present in a major vessel, resection was defined as non-curative. The resected specimens from 42 of the 142 patients were not suitable for microscopic evaluation, either because slides were not adequate for microsatellite evaluation or because slides did not show enough surrounding noncancerous tissue for evaluation. Excluding the 42 patients with unsuitable specimens, 100 consecutive patients were included in our retrospective study. All patients were followed up regularly at our outpatient clinic and monitored prospectively for disease recurrence by monthly assessment of serum tumor markers and by ultrasound or contrast computed tomography scans every 2-4 months.

The resected specimens were cut along the largest dimension of the hepatic tumor and fixed in 10% formalin. The specimens were then cut along the same plane into 5-mm-thick sections ($n = 1$ or 2). The sections were refixed in 10% formalin for 24 hours, embedded in paraffin, cut into 4- μ m-thick slices, and stained with hematoxylin and eosin. When multiple liver tumors, which were clinicopathologically considered a multicentric tumor, were surgically resected, the largest tumor was examined histologically. We reviewed all histologic slides to evaluate tumor grade (well, moderately, and poorly differentiated types defined by the Liver Cancer Study Group of Japan²⁰), invasion into the portal vein and intrahepatic metastasis, and presence of cirrhosis. Intrahepatic metastasis and multicentric cancer development were distinguished according to the definitions of the Liver Cancer Study Group of Japan.²⁰

The Liver Cancer Study Group of Japan defined intrahepatic metastases as tumors clearly growing from portal vein tumor thrombi, as tumors surrounding a large main tumor with multiple satellite nodules, and as small solitary tumors located near the main tumor and which are histologically similar or less differentiated than the main tumor. The Liver Cancer Study Group of Japan also defined multicentric occurrence as tumors separately registered as principal tumors that consisted of early, well differentiated HCC and as tumors of moderately and/or poorly differentiated HCC that have a margin of well differentiated HCC.

A microsatellite was defined as a microscopic invasion into the portal vein and/or intrahepatic metastasis¹¹ (Fig. 1), and the distance from the main HCC tumor to the most distant microsatellite was measured on the histologic slide. The longest measured distance was defined as the distance from the tumor to the microsatellite for each patient. Patients were divided into 3 groups according to microsatellite distance: 0 mm (no microsatellite), \leq 5 mm, and $>$ 5 mm.

We investigated 13 clinicopathologic variables pertaining to patient demographics, clinical data, and histopathologic findings (Table 1). The extent of surgical resection was defined according to Couinaud's segmentation scheme (i.e., limited hepatectomy comprised resection of less than one segment containing the main HCC tumor and anatomic hepatectomy comprised resection of more than one segment containing the main HCC tumor). All patient outcomes were determined by reference to clinical records as of April 30, 2003. The mean follow-up period for the 100 patients after hepatectomy was 47.3 months (median, 35.0 months; range, 1-166 months).

We investigated overall and disease-free survival af-

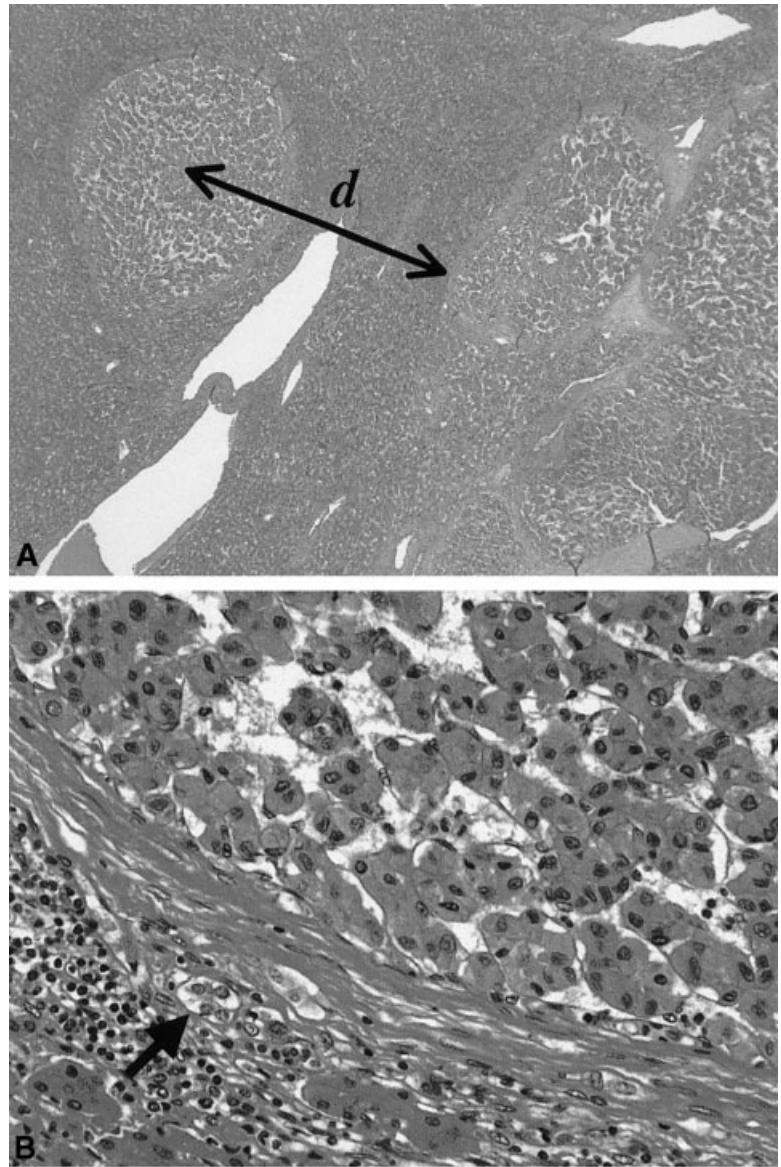


FIGURE 1. Microphotographs of intrahepatic metastasis of hepatocellular carcinoma (HCC) (hematoxylin/eosin stain). (A) The distance of invasion into the portal vein or intrahepatic metastasis from the main HCC tumor is measured (length of arrow). (B) The presence of the bile ductule (arrow) around the small HCC nodule suggests that the HCC tumor is growing from portal vein tumor thrombi. Original magnification $\times 20$ (A); $\times 200$ (B).

ter hepatectomy by univariate analysis. Data were censored when a patient remained alive or died of unrelated disease or cirrhosis-related disease (hepatic failure or ruptured esophagogastric varices). Data were censored in the analysis of disease-free survival when a patient remained alive or died of unrelated disease or cirrhosis-related disease without recurrent HCC. The association between microsatellite distance and clinicopathologic factors was evaluated by the chi-square or Fisher exact test for nominal variables, and by the Kruskal–Wallis test for continuous variables. Correlation between continuous variables not normally distributed was tested by the Spearman correlation coefficient (r). Linear regression lines were drawn by the least-square error method. Survival rates were calculated by the Kaplan–Meier method. Overall survival and disease-free survival curves were

drawn according to microsatellite distance and checked by the log-rank test. The survival rates were compared statistically by univariate test using the Cox proportional hazards model. Variables in which the P value for univariate analysis was < 0.1 were enrolled in the subsequent multivariate Cox proportional hazards model. $P < 0.05$ was significant in all analyses. Statistical analysis was performed with JMP software (JMP; SAS Institute, Inc., Cary, NC).

RESULTS
Clinicopathologic Characteristics

The patient group was comprised of 79 men and 21 women whose mean age at the time of hepatectomy was 64.1 years (range, 38–84 years). The mean tumor

TABLE 1
Relation between Microsatellite Distance and Clinicopathologic Factors

Clinical variables	No. of patients	Microsatellite			P value
		None	≤ 5 mm	> 5 mm	
Median no. of slides per case (range)	100	7 (2-18)	7 (2-15)	14.5 (5-31)	< 0.001
Gender					NS
Male	79	41	18	20	
Female	21	13	6	2	
Age (yrs)					NS
≤ 65	57	28	13	16	
> 65	43	26	11	6	
HBsAg level					NS
Negative	83	47	17	19	
Positive	17	7	7	3	
HCVAb level					NS
Negative	27	17	7	3	
Positive	59	33	13	13	
Cirrhosis					NS
Absent	44	28	6	10	
Present	56	26	18	12	
AFP level (nmg/ml)					< 0.001
≤ 20	46	33	7	6	
> 20	54	21	17	16	
Tumor size (mm)					< 0.05
< 25	24	17	6	1	
≥ 25	76	37	18	21	
Surgical procedure					< 0.05
Limited	60	34	18	8	
Anatomic	40	20	6	14	
Tumor grade					< 0.001
Well	21	21	0	0	
Moderately	74	32	23	19	
Poorly	5	1	1	3	
AST level (IU/L)					NS
≤ 40	33	19	9	5	
> 40	66	35	15	16	
ALT level (IU/L)					NS
≤ 40	35	22	7	6	
> 40	65	32	17	16	
Albumin level (mg/dL)					NS
≤ 3.5	21	12	7	2	
> 3.5	79	42	17	20	
ICG R ₁₅ (%)					NS
≤ 15	44	22	14	8	
> 15	54	31	9	14	
Platelet count (/mm ³)					NS
≤ 100,000	28	19	5	4	
> 100,000	72	35	19	18	

HBsAg: hepatitis B surface antigen; HCV Ab: hepatitis C virus antibody; AFP: α -fetoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ICG R₁₅: retention rate of indocyanine green at 15 minutes.

size was 33.9 mm (median, 34.0 mm; range, 10–50 mm) in greatest dimension, and patients had 1 ($n = 82$), 2 ($n = 15$), or 3 ($n = 3$) tumors. The mean number of slides for each patient that was histologically investigated was 9.6 (median, 8 slides; range 2–31 slides). The mean length between the main HCC tumor and the edge of the nonneoplastic liver tissue at the longest distance was 35.5 mm (median, 28.5 mm; range, 8–140 mm). Of 100 patients, 39 showed microscopic invasion of HCC cells into the portal vein and 24 showed intrahepatic metastasis, and 46 patients showed ≥ 1 microsatellite. The mean microsatellite distance from the main HCC tumor was 9.9 mm (median, 5.0 mm; range, 1–42 mm). There were 55 patients in the 0-mm (no microsatellite) group, 24 in the ≤ 5 -mm group, and 22 in the > 5 -mm group. The relations between these classifications and the clinicopathologic factors studied are shown in Table 1. Hepatitis B surface antigen and hepatitis C virus antibody were detected in 17.0% and 68.6% of the 100 patients, respectively. There was no correlation between the type of hepatitis virus infection and microsatellite distance. Forty-six patients showed a serum level of α -fetoprotein (AFP) within the normal range. Microsatellites occurred less frequently among these patients than among those with an elevated serum level of AFP. Anatomic resection was performed frequently in patients in the > 5 -mm microsatellite group. The mean weight of the resected liver specimen was 179 g in the 0-mm group, 140 g in the ≤ 5 -mm microsatellite group, and 326 g in the > 5 -mm microsatellite group. The median number of slides reviewed per patient was 7 (range, 2–18 slides) in the 0-mm (no microsatellite) group, 7 (range, 2–15 slides) in the ≤ 5 -mm microsatellite group, and 14.5 (range, 5–31 slides) in the > 5 -mm microsatellite group. The weight of the resected liver specimen and the number of slides per patient were significantly higher in the > 5 -mm microsatellite group than in the other 2 groups ($P < 0.01$). All microsatellites occurred in patients with one or more high-grade (moderate or poorly differentiated) HCC tumors. The preoperative levels of serum aspartate aminotransferase, alanine aminotransferase, albumin, platelet count, and the preoperative retention rate of indocyanine green at 15 minutes were not found to be correlated with microsatellite presence or distance.

Correlation between Tumor Size and Microsatellite Distance from the Main Hepatocellular Carcinoma Tumor
Tumor size and the distance of the microsatellite from the main HCC tumor were found to be significantly correlated ($r = 0.151$, $P < 0.001$; Fig. 2). There were 22 patients with HCC in the > 5 -mm microsatellite

FIGURE 2. Correlation between tumor size and distance to the microsatellite. The tumor size and the distance from the main tumor to the microsatellite are significantly correlated ($P < 0.001$). Microsatellites are not observed in well differentiated hepatocellular carcinoma (HCC) (“x”). There were 22 patients in the > 5-mm microsatellite group, 21 of whom had moderately (open circles) to poorly (open squares) differentiated HCC tumors measuring > 25 mm in greater dimension.

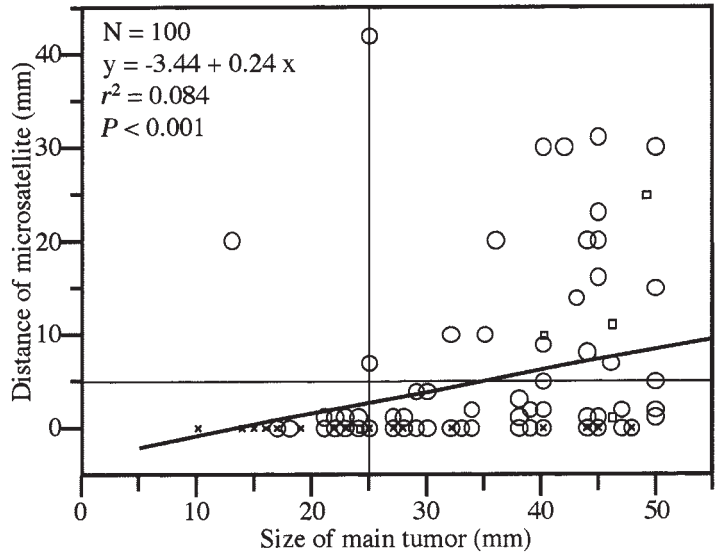


TABLE 2
Correlation between Tumor Size and Microsatellite Distance in Patients with HCC \geq 25 mm in Dimension

Tumor grade	Microsatellite			Total
	None	\leq 5 mm	> 5 mm	
Well differentiated	13	0	0	13
Moderately differentiated	24	17	18	59
Poorly differentiated	0	1	3	4
Total	37	18	21	76

HCC: hepatocellular carcinoma.

group, and 21 of them had a tumor \geq 25 mm in greatest dimension. All 21 tumors were high-grade (moderately to poorly differentiated) HCCs. There were 76 patients with an HCC tumor \geq 25 mm in greatest dimension (13 well differentiated, 59 moderately differentiated, and 4 poorly differentiated). There were 63 patients with a high-grade (moderate to poorly differentiated) tumor: 24 (38.1%) in the 0-mm (no microsatellite) group, 18 (28.6%) in the \leq 5-mm microsatellite group, and 21 (33.3%) in the > 5-mm microsatellite group (Table 2).

Overall and Disease-Free Survival

Of the 100 patients, 43 remained alive and 57 died by April 30, 2003. The causes of death were HCC ($n = 40$), liver failure related to cirrhosis ($n = 10$), ruptured esophageal varices ($n = 1$), and unrelated disease (pneumonia, cancer of another organ, asthma, or suicide; $n = 7$). The overall and disease-free survival curves are shown in Figure 3. The 5-year overall and disease-free survival rates of the 100 patients were 55.6% and 26.8%, respec-

tively. The overall 5-year survival rates were 75.9% in the 0-mm (no microsatellite) group, 54.1% in the \leq 5-mm microsatellite group, and 20.5% in the > 5-mm microsatellite group. The > 5-mm microsatellite group showed a significantly poor outcome in comparison to the other 2 microsatellite groups ($P < 0.01$ for both). The 5-year disease-free survival rates were 27.6% in the 0-mm (no microsatellite) group, 27.8% in the \leq 5-mm microsatellite group, and 23.8% in the > 5-mm microsatellite group. The disease-free survival rate of the > 5-mm microsatellite group was significantly lower than that of the 0-mm (no microsatellite) group ($P = 0.03$). However, there was no significant difference between the \leq 5-mm and the > 5-mm microsatellite groups ($P = 0.48$).

Univariate analysis revealed that male gender, elevated preoperative serum level of AFP, large tumor size, distance of microsatellites, and higher tumor grade were negative prognostic factors for overall survival after hepatic resection. Multivariate analysis revealed that male gender (relative risk [RR], 1.70; 95% confidence interval [95% CI], 1.11–2.85), elevated preoperative serum level of AFP (RR, 2.00; 95% CI, 1.37–3.08), and distance of microsatellite (RR, 1.07; 95% CI, 1.04–1.11) were associated significantly with overall survival after hepatic resection (Table 3). With respect to disease-free survival, male gender ($P = 0.06$) and elevated preoperative serum level of AFP ($P < 0.01$) were identified as adverse prognostic factors by univariate analysis. Multivariate analysis indicated that male gender (RR, 1.45; 95% CI, 1.05–2.09) and elevated preoperative serum level of AFP (RR, 1.45; 95% CI, 1.13–1.89) were significant factors for disease recurrence after hepatic resection.

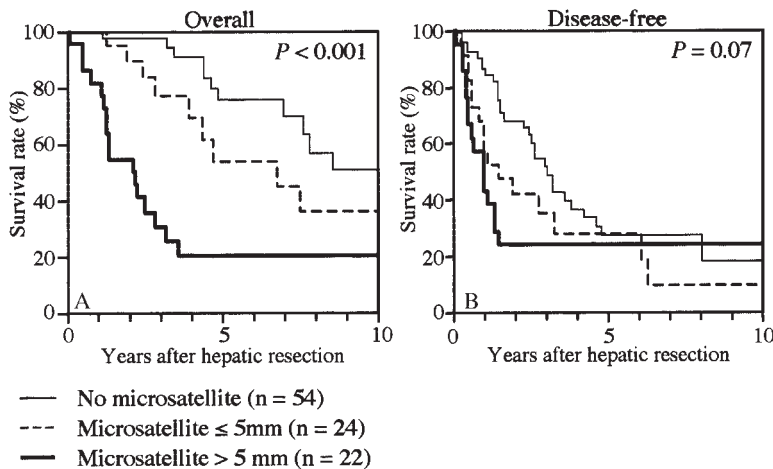


FIGURE 3. Overall (A) and disease-free (B) survival curves according to microsatellite distance. The > 5-mm microsatellite group demonstrated a lower survival rate compared with the 0-mm (no microsatellite) and the ≤ 5-mm groups. The disease-free survival rate of the > 5-mm microsatellite group was significantly lower than that of the 0-mm (no microsatellite) group ($P = 0.03$). However, there was no significant difference noted between the ≤ 5-mm and the > 5-mm microsatellite groups ($P = 0.48$).

DISCUSSION

Among risk factors for HCC recurrence, tumor size, portal vein invasion, and intrahepatic metastasis are generally considered the major causes of intrahepatic HCC recurrence after hepatectomy.^{8,21,22} Several studies address the relation between microvascular invasion of HCC cells and tumor size. Esnaola et al.⁹ found the frequency of microvascular invasion to be 25%, 31%, and 50% for tumors < 2 cm, 2–4 cm, and > 4 cm in greatest dimension, respectively. Okusaka et al.¹¹ showed microvascular invasion in 17% of patients with a tumor < 2 cm and in 20% of patients with a tumor 2–3 cm in dimension. In contrast, Tsai et al.⁸ showed an increased incidence of microvascular invasion: 40.5% in patients with a tumor < 2 cm, 49.6% in patients with a tumor 2–4 cm, and 58.1% in patients with a tumor 4–6 cm in dimension. The reported frequency of microvascular invasion in patients with an HCC tumor of 3–5 cm ranges from approximately 30–50%. In the current study, all tumors were < 5 cm in dimension and microscopic invasion into the portal vein occurred in 39% and intrahepatic metastasis occurred in 24% of patients.

To our knowledge, only a few investigators to date have reported a correlation between the distance of the microsatellite from the main HCC tumor and clinicopathologic factors. Lai et al.¹⁰ investigated 23 resected HCC tumor specimens (range, 1.7–18.1 cm in diameter) and measured the distance between microsatellite lesions and the main tumor. They reported that the distance to the microsatellite ranged from 0.1–71 mm and demonstrated that the presence of a large HCC (≥ 5 cm), multinodular lesions, macroscopic venous tumor thrombus, liver invasion, and nonencapsulated dominant nodules were associated positively with distance from the microsatellite to the main HCC tumor. Okusaka et al.¹¹ investigated 149

patients with HCC tumors ≤ 30 mm in dimension. They reported a distance from the microsatellite to the main HCC tumor ranging from 1 mm to 20 mm. They showed that no identifiable factors were related significantly to the distance from the main tumor to the microsatellite lesion. However, all microsatellite lesions located > 1.0 cm from the main tumor occurred with poorly differentiated HCC tumors, either the single nodular type with extranodular growth or the confluent multinodular type. In the current study, the preoperative serum level of AFP and tumor grade were found to be correlated with the presence or absence of microsatellites, and the distance from the microsatellite to the main HCC tumor was correlated positively to tumor size but no other clinicopathologic factor was investigated.

The adequate surgical margin for surgical management of HCC has been studied by hepatobiliary surgeons and remains controversial. Some studies showed that a width of the surgical margin of > 10 mm is related to outcome after hepatic resection.^{22–24} However, other studies indicate that the width of the resected margin is not a significant indicator of disease recurrence after hepatectomy for HCC.^{25–27} In studies showing the importance of the surgical margin, the mean tumor size was relatively small. For example, the mean tumor size was 3.4 cm in dimension in a report from Yoshida et al.,²³ and only approximately 40% of patients had an HCC tumor > 5 cm in dimension in a report from the Liver Cancer Study Group of Japan.²² In most studies in which the width of the surgical margin was considered less important, greater than half of the patients had an HCC tumor > 5 cm in diameter.^{25,26} We agree with Poon et al.²⁶ that most intrahepatic HCC recurrences arise from intrahepatic metastasis by means of venous dissemination, which cannot be prevented by a wide resection

TABLE 3
Results of Univariate and Multivariate Analyses of Clinicopathologic Factors for Overall Survival Rate after Hepatic Resection

Clinical variables	Univariate		Multivariate	
	RR(95% CI)	P value	RR (95% CI)	P value
Gender		0.04		0.01
Male	1.52(1.01-2.49)		1.70(1.11-2.85)	
Female	1		1	
Age (yrs)		0.50		
≤ 65	1.13(0.80-1.64)			
> 65	1			
HBsAg level		0.45		
Negative	1.37(0.63-3.40)			
Positive	1			
Cirrhosis		0.56		
Absent	1			
Present	1.10(0.80-1.55)			
AFP level (ng/ml)		< 0.01		< 0.01
≤ 20	1		1	
> 20	1.77(1.25-2.65)		2.00(1.37-3.08)	
Tumor size (mm)	1.03(1.00-1.06)	0.04	1.01(0.99-1.05)	0.32
Microsatellite (mm)	1.06(1.04-1.09)	< 0.01	1.07(1.04-1.11)	< 0.01
Surgical procedure		0.26		
Limited	1			
Anatomic	1.21(0.87-1.66)			
Tumor grade		0.04		0.86
Well	1		1	
Moderately/poorly	1.58(1.03-2.71)		1.05(0.65-1.86)	
AST level (IU/L)		0.36		
≤ 40	1			
> 40	1.17(0.84-1.70)			
ALT level (IU/L)		0.96		
≤ 40	1			
> 40	1.01(0.73-1.44)			
Albumin level (mg/dL)		0.75		
≤ 3.5	1.06(0.72-1.49)			
> 3.5	1			
ICG R15 (%)		0.12		
≤ 15	1			
> 15	1.29(0.93-1.80)			
Platelet count (/mm ³)		0.53		
≤ 100,000	1			
> 100,000	1.12(0.80-1.09)			

HBsAg: hepatitis B surface antigen; AFP: α -fetoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ICG R₁₅: retention rate of indocyanine green at 15 minutes.
 RR: relative risk; 95% CI: confidence interval.

margin in patients with a large HCC tumor. In a large series of the Liver Cancer Study Group of Japan,²² the patients had relatively small HCC tumors and underwent only partial hepatic resection, and the narrow surgical margin adversely influenced patient survival by univariate analysis. These results suggest that the distance of microvascular invasion from the main HCC tumor might be correlated with tumor size. In the current study, the distance of microsatellites from

the main HCC tumor correlated positively with tumor size. HCC tumors > 25 mm in greatest dimension with moderate to poor differentiation were likely to have microsatellites at a distance > 5 mm from main HCC tumor. The results of the current study suggest that the prognostic significance of surgical margins for disease recurrence after hepatic resection depends on tumor size. High-grade HCC tumors 25–50 mm in greatest dimension should be removed with adequate surgical margins.

To our knowledge, the indications for locoregional therapy, including PEI, MCT, and RFA, have not been clearly defined. It is generally agreed that patients with HCC tumors ≤ 3 cm in greatest dimension and with ≤ 3 tumors are the best candidates for PEI,^{3,12,16,17} although many centers perform PEI for patients with HCC tumors ≤ 5 cm.^{3,16} Many reports indicate that tumor size is a risk factor for intrahepatic disease recurrence after PEI.^{12,16,17,28} Unsuccessful PEI therapy for larger HCC tumors may result from the growth of small intrahepatic metastases adjacent to the main lesion that are not detected in the pretreatment staging work.^{16,17} Indications for MCT and RFA are controversial because these therapies have a high rate of local control in comparison to PEI.^{29,30} The development of these new modalities offers a nonsurgical treatment option for patients with large HCC tumors.^{18,31} In most investigations of thermal ablation, the definition of local or distant disease recurrence in the liver is not clear. Therefore, the disease recurrence rate due to microvascular invasion and/or intrahepatic metastasis from the main HCC tumor is not accurately reported. In the current and previous studies,^{10,11} the distance between the microsatellite and main HCC tumor < 5 cm in greatest dimension ranged from 1–42 mm. These results suggest that some HCC tumors < 5 cm might not be controllable by locoregional therapy including limited hepatectomy, PEI, MCT, and RFA.

In the current study, the postoperative cancer-related survival rate was found to be significantly lower in the patients in the > 5-mm group than in patients in the ≤ 5-mm microsatellite group ($P < 0.01$), despite the finding that the disease-free survival rate did not differ significantly between the 2 groups ($P = 0.48$). The slope of the disease-free survival curve decreased gradually across the microsatellite groups. As shown in Table 1, clinicopathologic factors, excluding tumor size, that were possible risk factors for HCC recurrence after hepatic resection (i.e., gender, age, preoperative liver function, serum level of AFP, and surgical procedure) did not differ between the > 5-mm and the ≤ 5-mm microsatellite groups. This suggests either that the malignant potential of the

HCC tumors in the > 5-mm microsattellite group is high, or that therapies for recurrent tumors may be less effective for these patients.

We conclude that in patients with low-grade HCC tumors or with tumors < 25 mm in greatest dimension, locoregional therapy (including limited resection ethanol injection and thermal ablation) is appropriate.

REFERENCES

1. Bosch FX, Ribes J, Borrás J. Epidemiology of primary liver cancer. *Semin Liver Dis.* 1999;19:271-285.
2. Tsukuma H, Hiyama T, Tanaka S, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. *N Engl J Med.* 1993;328:1797-1801.
3. Poon RTP, Fan ST, Tsang FHF, Wong J. Locoregional therapies for hepatocellular carcinoma: a critical review from the surgeon's perspective. *Ann Surg.* 2002;235:466-486.
4. Kojiro M. Pathology of early hepatocellular carcinoma: progression from early to advanced. *Hepatogastroenterology.* 1998;45:1203-1205.
5. Yuki K, Hirohashi S, Sakamoto M, Kanai T, Shimosato Y. Growth and spread of hepatocellular carcinoma: a review of 240 consecutive autopsy cases. *Cancer.* 1990;66:2174-2179.
6. Sasaki A, Aramaki M, Kawano K, et al. Intrahepatic peripheral cholangiocarcinoma: mode of spread and choice of surgical treatment. *Br J Surg.* 1998;85:1206-1209.
7. Sasaki A, Aramaki M, Kawano K, Yasuda K, Inomata M, Kitano S. Prognostic significance of intrahepatic lymphatic invasion in patients with hepatic resection due to metastases from colorectal carcinoma. *Cancer.* 2002;95:105-111.
8. Tsai TJ, Chau GY, Lui WY, et al. Clinical significance of microscopic tumor venous invasion in patients with resectable hepatocellular carcinoma. *Surgery.* 2000;127:603-608.
9. Esnaola NF, Lauwers GY, Mirza NQ, et al. Predictors of microvascular invasion in patients with hepatocellular carcinoma who are candidates for orthotopic liver transplantation. *J Gastrointest Surg.* 2002;6:224-232.
10. Lai ECS, You KT, Ng IOL, Shek TWH. The pathological basis of resection margin for hepatocellular carcinoma. *World J Surg.* 1993;17:786-791.
11. Okusaka T, Okada S, Ueno H, et al. Satellite lesions in patients with small hepatocellular carcinoma with reference to clinicopathologic features. *Cancer.* 2002;95:1931-1937.
12. Hasegawa S, Yamasaki N, Hiwaki T, et al. Factors that predict intrahepatic recurrence of hepatocellular carcinoma in 81 patients initially treated by percutaneous ethanol injection. *Cancer.* 1999;86:1682-1690.
13. Yamamoto J, Okada S, Shimada K, et al. Treatment strategy for small hepatocellular carcinoma: comparison of long-term results after percutaneous ethanol injection therapy and surgical resection. *Hepatology.* 2001;34:707-713.
14. Izumi N, Asahina Y, Noguchi O, et al. Risk factors for distant recurrence of hepatocellular carcinoma in the liver after complete coagulation by microwave or radiofrequency ablation. *Cancer.* 2001;91:949-956.
15. Komorizono Y, Oketani M, Sako K, et al. Risk factors for local recurrence of small hepatocellular carcinoma tumors after a single session, single application of percutaneous radiofrequency ablation. *Cancer.* 2003;97:1253-1262.
16. Lencioni R, Bartolozzi C, Caramella D, Palicchi A, et al. Treatment of small hepatocellular carcinoma with percutaneous ethanol injection: analysis of prognostic factors in 105 Western patients. *Cancer.* 1995;76:1737-1746.
17. Ishii H, Okada S, Nose H, et al. Local recurrence of hepatocellular carcinoma after percutaneous ethanol injection. *Cancer.* 1996;77:1792-1796.
18. Curley SA, Izzo F, Ellis LM, Vauthey JN, Vallone P. Radiofrequency ablation of hepatocellular cancer in 110 patients with cirrhosis. *Ann Surg.* 2000;232:381-391.
19. Lau WY, Leung TWT, Yu SCH, Ho SKW. Percutaneous local ablative therapy for hepatocellular carcinoma: a review and look into the future. *Ann Surg.* 2003;237:171-179.
20. The Liver Cancer Study Group of Japan. Classification of primary liver cancer. 1st English ed. Tokyo: Kanehara & Co., Ltd.
21. Izumi R, Shimizu K, Ii T, et al. Prognostic factors of hepatocellular carcinoma in patients undergoing hepatic resection. *Gastroenterology.* 1994;106:720-727.
22. The Liver Cancer Study Group of Japan. Predictive factors for long term prognosis after partial hepatectomy for patients with hepatocellular carcinoma in Japan. *Cancer.* 1994;74:2772-2780.
23. Yoshida Y, Kanematsu T, Matsumata T, Takeneka K, Sugimachi K. Surgical margin and recurrence after resection of hepatocellular carcinoma in patients with cirrhosis: further evaluation of limited hepatic resection. *Ann Surg.* 1989;209:297-301.
24. Lise M, Bacchetti S, Pian PD, Nitti D, Pilati PL, Pigato P. Prognostic factors affecting long term outcome after liver resection for hepatocellular carcinoma: results in a series of 100 Italian patients. *Cancer.* 1998;82:1028-1036.
25. Jwo SC, Chiu JH, Chau GY, Loong CC, Lui WY. Risk factors linked to tumor recurrence of human hepatocellular carcinoma after hepatic resection. *Hepatology.* 1992;16:1367-1371.
26. Poon RTP, Fan ST, Ng IOL, Wong J. Significance of resection margin in hepatectomy for hepatocellular carcinoma: a critical reappraisal. *Ann Surg.* 2000;231:544-551.
27. Yamamoto J, Kosuge T, Takayama T, et al. Recurrence of hepatocellular carcinoma after surgery. *Br J Surg.* 1996;83:1219-1222.
28. Vilana R, Bruix J, Bru C, Ayuso C, Solé M, Rodés J. Tumor size determines the efficacy of percutaneous ethanol injection for the treatment of small hepatocellular carcinoma. *Hepatology.* 1992;16:353-357.
29. Seki T, Wakabayashi M, Nakagawa T, et al. Percutaneous microwave coagulation therapy for patients with small hepatocellular carcinoma: comparison with percutaneous ethanol injection therapy. *Cancer.* 1999;85:1694-1702.
30. Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. *Radiology.* 1999;210:655-661.
31. Livraghi T, Goldberg SN, Lazzaroni S, et al. Hepatocellular carcinoma: radio-frequency ablation of medium and large lesions. *Radiology.* 2000;214:761-768.