Original Article

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Comparison of the surgical outcomes in patients with synchronous versus metachronous multiple hepatocellular carcinoma

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SUMMARY Multiplicity is one of the characteristics of hepatocellular carcinoma (HCC), and patients with multiple HCC (≤ 3 nodules) are recommended as candidates for liver resection. To confirm the validity of resecting multiple HCC, we compared the surgical outcomes in patients with synchronous and metachronous multiple HCC. Patients who underwent resection for multiple HCC (2 or 3 nodules) were classified into the "synchronous multiple HCC" group, while those undergoing resection for solitary HCC and repeated resection for 1 or 2 recurrent nodules within 2 years after initial operation were classified into the "metachronous multiple HCC" group. After one-to-one matching, longer operation time and more bleeding were seen in the synchronous multiple HCC group (n = 98) than those in the metachronous multiple HCC group (n = 98); however, the complication rates were not different between the two groups. The median overall survival times were 4.0 years (95% CI, 3.0-5.9) and 5.9 years (4.0-NA) for the synchronous and metachronous multiple HCC (after second operation) groups, respectively (P = 0.041). The recurrence-free survival times were shorter in the synchronous multiple HCC group than in the metachronous multiple HCC group (median, 1.5 years [95% CI, 0.9-1.8] versus 1.8 years, [1.3-2.2]) (P = 0.039). On multivariate analysis, independent factors for overall survivals in the synchronous multiple HCC group were older age, cirrhosis, larger tumor, and tumor thrombus. Taken together, resection of metachronous multiple HCC still has good therapeutic effect, even better than synchronous multiple HCC, so resection is suggested for metachronous multiple HCC.

Keywords multiple hepatocellular carcinoma, patient stratification, guideline

1. Introduction

Multiplicity is one of the characteristics of hepatocellular carcinoma (HCC) (*1*), and patients with multiple HCC, classified as the intermediate stage (B) in the Barcelona-Clinic Liver Cancer staging classification, are candidates for transcatheter arterial chemoembolization (TACE) (*2*). In contrast, the survival benefit of liver resection for multiple HCC has been reported (*3-5*); survival of patients undergoing liver resection for such nodules was longer than that of patients undergoing TACE according to a nationwide study (*6*) and a prospective study (*7*). Consequently, resection of multiple HCC ≤ 3 is indicated by clinical practice guidelines for hepatocellular carcinoma in Japan (*8*).

However, the surgical outcomes of patients with multiple HCC after resection were worse than those of patients with solitary nodule even if they met the criteria regarding the number of tumors and liver function (*9,10*). Therefore, patients with multiple HCC should not be treated in the same way, but should be stratified for determination of the candidates of liver resection.

Multiple HCC consist of primary HCC and its metastatic nodules or new lesions (*11-13*); therefore, multiple HCC can be considered as having "synchronous multiple HCC". On the other hand, patients with recurrent HCC could be considered as having other nodules after resection of primary HCC; therefore, such patients can be considered as having "metachronous multiple HCC" (*14*). Besides of synchronous multiple HCC, therefore, solitary HCC harbors the potential of multiplicity.

In this study, we compared the surgical outcomes of patients with synchronous multiple HCC to those of patients with metachronous multiple HCC after propensity matching and identified the types of multiple HCC patients that were good candidates for liver resection.

2. Patients and Methods

2.1. Patients

Patients who underwent initial and curative resection of HCC between 2000 and 2018 at the Nihon University Itabashi Hospital (Tokyo, Japan) were included in this study. Each participant provided written informed consent, and this study was approved by the review board of Nihon University. All clinical investigations were conducted according to the principles of the Declaration of Helsinki.

2.2. Multiple HCC

Patients who underwent liver resection for multiple HCC (2 or 3 nodules) were defined as "synchronous multiple HCC". In contrast, patients who underwent liver resection for solitary HCC and repeated resection for 1 or 2 recurrent nodules were defined as "metachronous multiple HCC". Considering the malignant potential of multiple nodules, patients who showed recurrence 2 years after the initial operation were excluded from the metachronous HCC group. Survival after the first operation for the synchronous multiple HCC group and that after the second operation for the metachronous multiple HCC group were compared after propensity-score matching to adjust for patient background, liver function, and tumor status, including age, sex, hepatitis viral infection, alcohol abuse, diabetes mellitus, varices, Child-Pugh classification, indocyanine green clearance rate at 15 min (ICGR15), background liver, and status of the main tumor. Considering that the tumor number was different during the operation between the two groups, tumor markers were not included as covariates. Propensity scores were matched using a caliper width of 0.2, and one-to-one pair matching was performed.

2.3. Indications for liver resection

The indications for liver resection and other treatments for patients with HCC were determined by assessing their liver functional reserve according to the Guidelines on Liver Cancer Examination and Treatment in Japan (*8*). Briefly, patients with Child-Pugh A or B with up to 3 lesions were candidates for liver resection.

2.4. Surgical procedure

Open liver resection was performed in all patients according to the criteria based on the liver function (*15*). The liver was transected under ultrasonographic guidance using the clamp-crushing method with the inflow-blood-occlusion technique (*16*). Curative resection was defined as the complete removal of recognizable viable HCC diagnosed preoperatively or intraoperatively with macroscopically tumor-free surgical margins. Postoperative complications were stratified according to the Clavien-Dindo classification (*17*), which defines morbidities as complications with a score of ≥ 3a. Complications specific to liver resection were defined as described previously (*18*).

2.5. Follow-up after operation

All patients were followed up to determine the postoperative recurrence as described previously (*19*). Briefly, levels of tumor markers, including alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP), were measured and imaging studies, including computed tomography and ultrasonography, were performed every 3 months in all patients. Recurrence was diagnosed by dynamic computed tomography and/or magnetic resonance imaging. The date of recurrence was defined as the date of examination when the recurrent HCC was noted.

2.6. Statistical analysis

Data collected from each group were statistically analyzed using the Fisher's exact test and Wilcoxon rank-sum test. Survival curves were generated using the Kaplan-Meier method and compared using the log-rank test. Prognostic factors for overall survival were identified using the Cox proportional hazards regression model. P value < 0.10 was set as the cut-off value for elimination. The following 16 variables, considered potential confounders, were examined: age (≥ *vs.* < 75 years), sex, positive result for hepatitis B and C viruses, alcohol abuse, diabetes mellitus, Child-Pugh classification (5 *vs.* 6 or 7), ICGR15 (≥ *vs.* < 15%), esophageal varices, serum AFP level (≥ *vs.* < 100 ng/mL), serum DCP level (≥ *vs.* < 100 mAU/mL), and pathological findings of the main tumor (maximal tumor size [≥ *vs.* < 3.0 cm], vascular invasion of tumor, liver cirrhosis, tumor differentiation grade [poorly vs well and moderately], and surgical margin). P values < 0.05 were considered to indicate significance.

3. Results

3.1. Patients

A total of 1,244 patients underwent initial and curative resection of HCC. After excluding 39 patients with four or more nodules, 1,205 patients were classified as those with multiple nodules (2 or 3 nodules) (the synchronous multiple HCC group, n = 280) and those with solitary HCC (n = 925). After excluding 493 patients who showed no recurrence within 2 years and 323 patients who did not undergo liver resection for recurrent HCC, the remaining 109 patients were classified as the metachronous multiple HCC group (Figure 1). The median of disease-free interval from the initial

operation in the metachronous multiple HCC group was 1.3 years (range, 0.2-1.9 years).

Before propensity-score matching, more patients were males (P = 0.020) and had higher serum DCP level (P = 0.025), larger main tumor (P = 0.001), and more frequent liver cirrhosis (P = 0.017) in the synchronous multiple HCC group (Table 1).

3.2. Operative data

After one-to-one matching, the operation time was longer (P = 0.039) with more bleeding (P = 0.015) in the synchronous multiple HCC group (n = 98) than that in the metachronous multiple HCC group (n = 98) owing to the number of resected tumors (Table 2). The postoperative stay was longer in the synchronous multiple HCC group (P < 0.001). The frequencies of overall complications and morbidities were not significantly different between the two groups. One patient in the synchronous multiple HCC group underwent re-operation for intraperitoneal abscess, and three patients in the metachronous multiple HCC group for intraperitoneal hemorrhage (two patients) and bile leakage (one patient). There was no hospital death in this series.

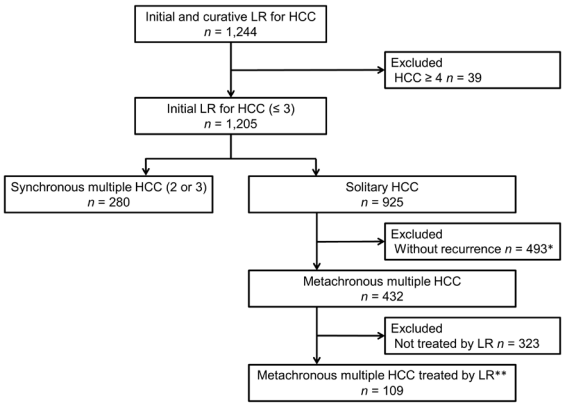

Figure 1. Flow diagram showing patient recruitment and follow-up. *, Including 88 patients with recurrence, 2 years after initial liver resection. **, Primary and recurrent HCC were treated by liver resection in these patients. LR, liver resection; HCC, hepatocellular carcinoma.

3.3. Survivals

After a median follow-up of 3.2 years (range, 0.2-12.8 years), a total of 150 patients (76.5%) had recurrence, and treatment for recurrent HCC did not differ between the two groups (Table 3). The median overall survival times were 4.0 years (95% confidence interval [CI], 3.0-5.9) and 5.9 years (4.0-NA) for the synchronous multiple HCC (n = 98) and metachronous multiple HCC (n = 98) (after second operation) groups, respectively (P = 0.041) (Figure 2A). The recurrence-free survival was shorter in the synchronous multiple HCC group (median, 1.5 years; 95% CI, 0.9-1.8) than that in the metachronous multiple HCC group (1.8 years, 1.3-2.4; P = 0.039) (Figure 2B). The 5-year-rates of overall survivals were 43.2% and 60.0% in the two groups, respectively, and those of recurrence-free survivals were 10.7% and 15.6%, respectively.

On multivariate analysis, the independent factors for overall survivals in the synchronous multiple HCC group (n = 280) were older age (hazard ration [HR], 1.57; 95% CI, 1.13-2.19, P = 0.006), liver cirrhosis (HR, 1.67; 1.12-2.48, P = 0.010), larger tumor (HR, 1.84; 95% CI, 1.30-

Table 1. Patient background

	Before propensity-score matching			After propensity-score matching		
	Synchronous (n = 280)	Metachronous (n = 109)	P	Synchronous (n = 98)	Metachronous (n = 98)	P
Age, years	69 (33-85)	68 (40-82)	0.341	67 (33-78)	68 (40-82)	0.597
Sex, male	236 (84.2)	80 (73.3)	0.020	76 (77.5)	77 (78.5)	1
Hepatitis B	43 (15.3)	20 (18.3)	0.540	16 (16.3)	17 (17.3)	1
Hepatitis C	152 (54.2)	56 (51.3)	0.651	56 (57.1)	52 (53.0)	0.666
Alcoholic	85 (30.3)	28 (25.6)	0.362	24 (24.4)	28 (28.5)	0.627
Diabetes mellitus	92 (32.8)	29 (26.6)	0.272	27 (27.5)	26 (26.5)	1
Child-Pugh, 5	214 (76.4)	83 (76.1)	1	75 (76.5)	74 (75.5)	1
ICGR15, %	13.2 (3.1-59.1)	12.6 (1.9-44.9)	0.726	12.8 (4.3-59.1)	12.8 (1.9-44.9)	0.691
Varices	64 (22.8)	24 (22.0)	0.893	21 (21.4)	21 (21.4)	1
Alpha fetoprotein, ng/mL	24 (1-211,062)	18 (1-541,432)	0.147	20 (1-211,602)	14 (1-541,432)	0.178
DCP, mAU/mL	108 (8-75,000)	44 (8-75,000)	0.025	71 (8-75,000)	44 (8-75,000)	0.287
Pathology†						
Tumor size, cm	3.5 (0.9-21.0)	2.7 (0.9-16.5)	0.001	3.1 (1.2-19.0)	2.9 (1.0-16.5)	0.297
Differentiation, por	42 (15.0)	10 (9.1)	0.139	12 (12.2)	11 (11.2)	1
Vascular invasion	89 (31.7)	43 (23.6)	0.058	30 (30.6)	26 (26.5)	0.635
Surgical margin, positive	20 (7.1)	9 (8.2)	0.673	9 (9.1)	8 (8.1)	1
Cirrhosis	116 (41.4)	31 (37.7)	0.017	32 (32.6)	31 (31.6)	1

Data are presented as median (range) or n (%). †, Histological findings of the main tumor. ICGR15, indocyanine green clearance rate at 15 minutes; DCP, desgamma-carboxy prothrombin.

Table 2. Operative data

	Synchronous (n = 98)	Metachronous (n = 98)	P
Operative time, min	346 (184-691)	328 (146-631)	0.039
Bleeding, mL	345 (25-2,988)	257 (15-1,900)	0.015
Transfusion	6 (6.1)	5 (5.1)	1
Complications			
Overall	40 (40.8)	30 (30.6)	0.179
Morbidity	30 (30.6)	22 (22.4)	0.257
Liver failure	1 (1.0)	0	
Intraperitoneal hemorrhage	0	2 (2.0)	
Bile leakage	2 (2.0)	3 (2.0)	
Intraperitoneal abscess	1 (1.0)	0	
Ascites	0	1 (1.0)	
Infection (Wound, Drainage tube)	14 (14.2)	5 (5.1)	
Respiratory	8 (8.1)	11 (11.2)	
Ileus	1 (1.0)	0	
Others	3 (3.0)	0	
Re-operation	1 (2.5)	3 (3.2)	0.621
Operative death	0	0	1
Hospital stay, days	14 (7-99)	12 (7-36)	< 0.001

Data are presented as median (range) or n (%). Data at the second operation for the patients with metachronous multiple HCC.

Table 3. Treatment for recurrent HCC

	Synchronous (n = 77)	Metachronous (n = 73)	P
Liver resection	25 (32.4)	30 (41.0)	0.311
Radiofrequency ablation	3 (3.8)	2 (2.7)	1
TACE/HAIC	43 (55.8)	36 (49.3)	0.513
Radiation	1 (1.2)	2 (2.7)	0.612
Chemotherapy	1 (1.2)	2 (2.7)	0.612
None	3 (3.8)	1 (1.3)	0.620

Data are presented as n (%). Data at the second operation for the patients with metachronous multiple HCC. TACE, transcatheter arterial chemoembolization; HAIC, hepatic arterial infusion chemotherapy

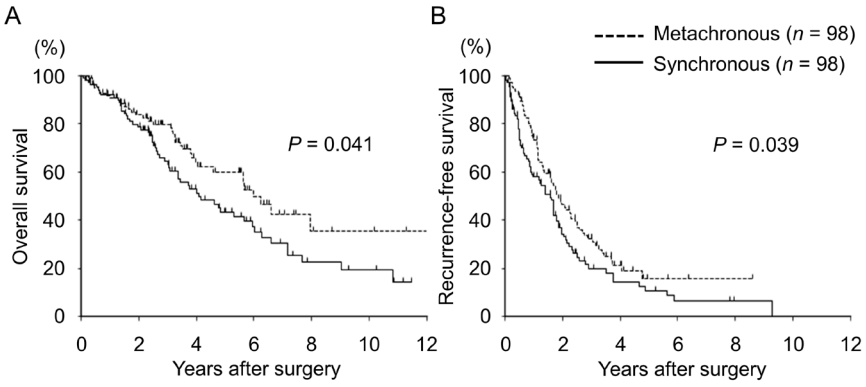

Figure 2. Survival of patients with multiple HCC. (A) Overall survival of patients in the synchronous multiple HCC group is significantly shorter than that of patients in the metachronous multiple HCC group (P = 0.041). **(B)** Recurrence-free survival of patients in the synchronous multiple HCC group is significantly shorter than that of patients in the metachronous multiple HCC group (P = 0.039).

2.63, P < 0.001), and tumor thrombus (HR, 1.42; 1.01-2.07, P = 0.041) (Table 4). The median overall survival times were significantly shorter in patients ≥ 70 years old (3.4 years [range, 3.0-4.1 years] versus 6.2 years [4.0-7.1 years], P = 0.022), those with cirrhosis (3.4 years [range, 3.0-4.1 years] versus 6.2 years [4.0-7.1 years], P = 0.006), and those with tumor ≥ 3.0 cm (3.4 years [range, 3.0-4.3 years] versus 5.6 years [4.1-6.6 years], P = 0.006), and shorter in patients with tumor thrombus (2.8 years [range, 2.1-4.0 years] versus 4.7 years [3.9-5.7 years], P = 0.074) (Figure 3).

4. Discussion

Our data showed that the survival of patients with synchronous multiple HCC after liver resection was

Table 4. Prognostic factors for survival of patients with synchronous multiple HCC

	Univariate			Multivariate		
	Hazard ratio	95% CI	*P*	Hazard ratio	95% CI	*P*
Age	1.44	1.05-1.99	0.023	1.57	1.13-2.19	0.006
Sex	0.91	0.61-1.41	0.684			
Hepatitis B	0.67	0.39-1.07	0.100			
Hepatitis C	0.91	0.66-1.25	0.575			
Alcohol	0.98	0.69-1.37	0.913			
Diabetes mellitus	0.86	0.61-1.21	0.408			
Child-Pugh	1.38	0.96-1.94	0.073	1.19	0.81-1.73	0.351
ICGR15	1.43	1.03-1.98	0.028	1.22	0.85-1.75	0.263
Varices	1.45	1.02-2.04	0.037	1.21	0.79-1.82	0.362
Alpha fetoprotein	0.98	0.67-1.39	0.924			
DCP	0.90	0.65-1.23	0.518			
Cirrhosis	1.55	1.12-2.13	0.006	1.67	1.12-2.48	0.010
Tumor size	1.57	1.13-2.19	0.006	1.84	1.30-2.63	< 0.001
Thrombus	1.35	0.96-1.88	0.080	1.42	1.01-2.07	0.041
Differentiation grade	1.14	0.81-1.61	0.444			
Surgical margin	0.80	0.35-1.55	0.549			

CI, confidence interval; ICGR15, indocyanine green clearance rate at 15 minutes; DCP, des-gamma-carboxy prothrombin.

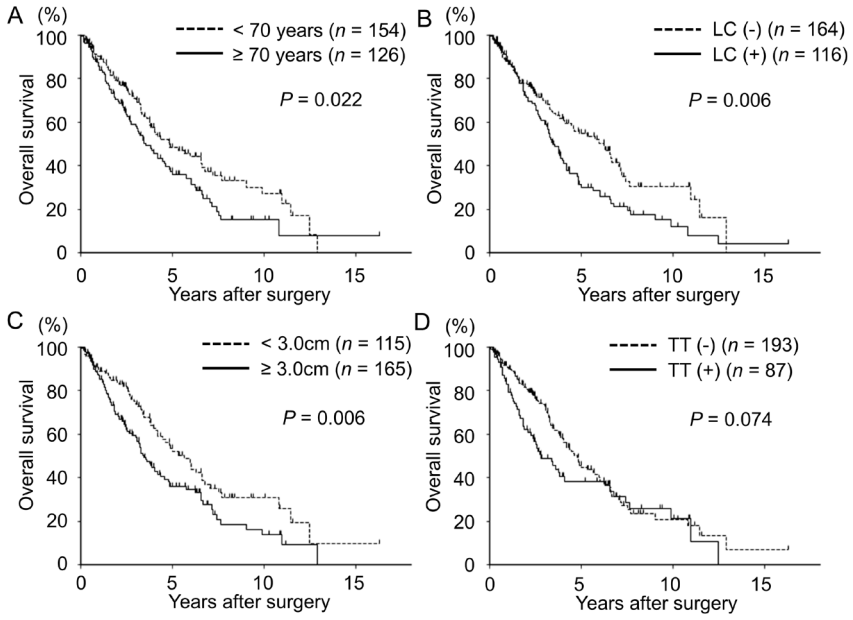

Figure 3. Overall survival of patients in the synchronous multiple HCC group. (A) Survival in patients ≥ 70 years of age versus that in patients < 70 years of age (P = 0.022). **(B)** Survival in patients with liver cirrhosis versus that in patients without cirrhosis (P = 0.006). **(C)** Survival in patients with the tumor ≥ 3.0 cm versus that in patients with the tumor < 3.0 cm (P = 0.006). **(D)** Survival in patients with tumor thrombus versus that in patients without tumor thrombus (P = 0.074). LC, liver cirrhosis; TT, tumor thrombus.

shorter than that of patients with metachronous multiple HCC. Therefore, patients with metachronous multiple HCC (≤ 3 nodules) are good candidates for resection (*20*).

We and others previously reported that surgical outcomes of patients with multiple HCC were worse than those of patients with solitary HCC (*9,10*). Many patients with solitary HCC were alive without recurrence for long periods after operation (*21-23*). In this study, we defined the tumors that recurred within 2 years after operation of solitary HCC as metachronous multiple HCC because such tumors harbor the potential of multiple nodules. We compared the surgical outcomes of patients with multiple HCC and those with solitary HCC with potential of multiplicity.

The survival times of the metachronous multiple HCC group was defined as the period from the date of second operation to that of recurrence or death, as usually applied for comparison of survivals between the synchronous and metachronous liver metastasis of colorectal cancer (*24,25*). This is because one of the tumors in the synchronous multiple HCC is an intrahepatic metastasis from the primary HCC or *de*

novo HCC, which develops after appearance of the primary HCC. Consequently, the surgical outcomes of patients with synchronous multiple HCC were worse than those even after recurrence in patients with solitary HCC.

The occurrence of multiple HCC can be explained by intrahepatic metastasis or multicentric origin (*11-13*). To adjust the two mechanisms of hepatocarcinogenesis between the synchronous and metachronous multiple HCC groups, only patients with the disease-free interval < 2 years were included in the latter group in this study. This could be because intrahepatic metastasis is observed within two years after initial resection in many patients with metachronous multiple HCC by genome analysis using a next-generation sequencer (*14,26*). Consequently, the solitary HCC patients who were cured by liver resection were excluded (*27*), and we assumed that the inclusion criteria regarding disease-free interval was appropriate.

The patient background differed between the two groups. As the metachronous multiple HCC group had candidates who underwent repeated resection of recurrent HCC, liver cirrhosis was less frequent before propensity matching. Consequently, the complication rates were higher in the synchronous multiple HCC group. Therefore, the complication rates were not different after matching of the background. The status of the main tumor was more advanced in the synchronous multiple HCC group, and tumor conditions may be matched between the two groups. On the other hand, tumor number was different between the two groups at the initial operation, which must affect the serum tumor marker levels; therefore, they were not matched in this series. Further, the synchronous multiple HCC group showed longer operation time and more bleeding even after propensity matching owing to the difference in the number of resected tumors.

On multivariate analysis, the survival of patients with synchronous multiple HCC was shorter in the older patients with larger tumors, tumor thrombus, and liver cirrhosis. Given that surgical outcomes of patients with multiple HCC are not preferable (*9,10*), the candidates for liver resection should be determined based on the patient background, tumor status, and liver function (*20*); however, studies have showed the superiority of liver resection to TACE for multiple HCC (*6,7*).

This study had several limitations. First, there is no consensus for definition of metachronous multiple HCC. For example, solitary HCC followed by recurrence within six months or one year might have been considered synchronous multiple HCC as in the metastasis of colorectal cancer. On the other hand, metachronous multiple HCC in this study was a counterpart of the synchronous multiple HCC; therefore, we defined the two types of multiple HCC in the Methods section. Next, this study was a retrospective study, and selection bias, especially in the determination of candidates for surgery for recurrent HCC, might have affected the surgical outcomes in the metachronous multiple HCC group. Finally, multiple HCC are divided into the two categories; intrahepatic metastasis and multicentric origin. However it is clinically difficult to distinguish between the two types of multiple HCC, and the frequencies of intrahepatic metastasis and multicentric origin in each group are unknown, which might affect the surgical outcomes in this study.

In conclusion, the surgical outcomes of patients with synchronous multiple HCC, usually same as "multiple HCC", were worse even after curative resection. By contrast, resection of metachronous multiple HCC still had good therapeutic effect, so resection is suggested for metachronous multiple HCC.

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