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Clinical Significance of Hepatectomy for Hepatocellular Carcinoma Associated with Extrahepatic Metastases

Shohei Komatsu Masahiro Kido Motofumi Tanaka Kaori Kuramitsu Daisuke Tsugawa Masahide Awazu Hidetoshi Gon Hiroaki Yanagimoto Hirochika Toyama Takumi Fukumoto

Department of Surgery, Division of Hepato-Biliary-Pancreatic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan

Keywords
Hepatocellular carcinoma · Distant metastasis · Lymph node metastasis · Hepatectomy

Abstract
Background: This study evaluated the prognosis of hepatocellular carcinoma (HCC) patients with extrahepatic metastases who can undergo hepatectomy. ***Methods:*** A total of 32 patients who underwent hepatectomy for HCC with extrahepatic metastases, including lymph node and/or distant metastases were recruited for this study. ***Results:*** Fourteen patients had lymph node metastasis only, 16 had distant metastasis only, and 2 had both metastasis types during preoperative diagnosis. The 3-year overall survival (OS) rate of all patients was 17.9%, and the median survival time (MST) was 11.8 months. Univariate analysis revealed that intrahepatic maximal tumor size, intrahepatic tumor number, and intrahepatic tumor control after hepatectomy were significant factors influencing OS ($p < 0.05$). Multivariate analysis revealed that independent risk factors for OS were intrahepatic maximal tumor size and intrahepatic tumor number ($p < 0.05$). The MST and 3-year OS rate of patients with maximal tumor size <100 mm and intrahepatic tumor number ≤2 were 39.0 months and 51.9%, respectively. ***Conclusions:*** Hepatectomy is not recommended for HCC patients with extrahepatic metastasis with ≥3 intrahepatic tumors, even when all intrahepatic tumors can be eliminated via hepatectomy. Aggressive surgery may be justified for HCC patients with ≤2 intrahepatic tumors and maximal tumor size <100 mm, irrespective of vascular invasion.

Introduction

Hepatocellular carcinoma (HCC) is among the most common cancer types in Asia, and its incidence is also increasing in Western countries [1]. HCC has a great propensity to invade the portal and hepatic veins, resulting in both intra- and extrahepatic metastases, well-known significant poor prognostic factors [2–6]. Extrahepatic metastases can be divided into lymph node and distant metastases, including lung metastases, peritoneal dissem-

karger@karger.com
www.karger.com/dsu

Dr. Shohei Komatsu
Kobe University Graduate School of Medicine
Department of Surgery, Division of Hepato-Biliary-Pancreatic Surgery
7-5-2 Kusunoki-cho, Chuo-ku, Kobe 650-0017 (Japan)
komasho8@med.kobe-u.ac.jp

ination, bone metastases, and adrenal gland metastases. In the American Joint Committee on Cancer (AJCC)/Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) staging system, regional lymph node metastasis (N1) and distant metastasis (M1) are classified separately, while the Barcelona Clinic Liver Cancer staging system does not differentiate between these 2 types of extrahepatic metastasis [7, 8].

Although the European and American Association for the Study of the Liver recommends multikinase inhibitors with antiangiogenic properties as the only treatment option for HCC patients with extrahepatic metastases, irrespective of the tumor status, their survival impact is quite limited [9, 10]. As there is great heterogeneity in tumor status in this patient population, the effectiveness of other treatment approaches is debatable, including hepatectomy for controlling intrahepatic tumors. Although several studies assessing surgical approaches for HCC with extrahepatic metastases have failed to demonstrate the efficacy of hepatectomy, the small sample size and/or the great heterogeneity in the patient population has precluded a definitive conclusion [11–13].

The rationale for HCC treatment of our team is that expeditious local control of intrahepatic tumors may prolong survival, as demonstrated in our case series [14–17]. The combined use of hepatectomy with locoregional treatment, including transcatheter arterial chemoembolization (TACE), transcatheter arterial infusion, and/or our original method of percutaneous isolated hepatic perfusion (PIHP), can potentially prolong survival, even with multiple intrahepatic and/or extrahepatic tumors. In HCC, huge tumors and severe vascular invasion (portal vein tumor thrombus and/or hepatic/inferior vena cava tumor thrombus) are oncologic emergencies; therefore, we first resect these life-threatening tumors that are difficult to treat with other locoregional treatments. Accordingly, the presence of distant and/or lymph node metastasis is not a contraindication for hepatectomy when intrahepatic tumors are crucial prognostic factors. Therefore, the aim of the present study was to identify reliable clinical parameters that could be used for better selection of HCC patients with extrahepatic metastases to undergo hepatectomy.

Patients and Methods

Study Population

Between January 2000 and December 2015, 594 patients with HCC underwent initial hepatectomy at Kobe University Hospital. Their clinicopathological data were retrieved from our prospectively collected database, and tumors were staged by using the AJCC/UICC TNM 7th staging system [7]. The study population included 32 patients who underwent hepatectomy for HCC with extrahepatic metastases, including lymph node and/or distant metastases, according to the preoperative diagnosis. Postoperative complications were classified according to the Clavien-Dindo classification [18], and complications ≥grade III were considered severe. This study was conducted according to the ethical standards of the Declaration of Helsinki and approved by the Ethics Committee of Kobe University in 2018 (approval number #180092). All patients provided written informed consent before the initiation of treatment.

All patients underwent preoperative laboratory blood tests, including the viral serology test, and measurements of the levels of serum alpha-fetoprotein (AFP), serum protein induced by vitamin K absence or antagonist II (PIVKAII), serum albumin, and total bilirubin, as well as the prothrombin time. Liver function was assessed by using the Child-Pugh classification, indocyanine green test, and 99mTc-galactosyl human serum albumin scintigraphy. Tumor characteristics were evaluated using routine triple-phase contrast-enhanced thoracic and abdominal computed tomography, transabdominal ultrasonography, magnetic resonance imaging, and angiography.

Inclusion Criteria and Study Design

Patients were selected for undergoing hepatectomy if they fulfilled the following criteria: (i) absence of prohibitive comorbidities, (ii) Child-Pugh class A or B liver function, and (iii) if macroscopic resection of the targeted tumor could be planned with sufficient future remnant liver volume upon preoperative computed tomography scan volumetry. Hepatectomy was indicated for HCC with lymph node and/or distant metastases only when hepatectomy could eliminate the most conceivable poor prognostic factor by resecting the main tumor. Subsequent local treatments include our original PIHP, TACE/transcatheter arterial infusion, radiofrequency ablation, and radiotherapy (conventional photon and particle therapy). When selecting subsequent treatments after reductive hepatectomy, PIHP was proactively introduced if the situation permitted; otherwise, the most appropriate treatments were selected considering the patient's performance status, liver function, and tumor factors.

Prognostic factors for survival were evaluated for all 32 patients with lymph node and/or distant metastases. Detailed analyses of each population, that is, HCC patients with lymph node metastasis and those with distant metastasis, were conducted.

Surgical Procedure and Diagnosis of Extrahepatic Metastases

Hepatectomy in all patients was performed using a right subcostal open approach. Intraoperative exploration and ultrasonography were performed routinely to confirm the extent of liver tumor and extrahepatic dissemination. Parenchymal transection of the liver was performed using the Cavitron ultrasonic surgical aspirator via the Pringle maneuver.

The diagnoses of lymph node or distant metastasis in the present study were based on the findings on preoperative imaging. When lymph node and distant metastases were resectable, they were resected simultaneously via hepatectomy. Pathologic specimens of the liver were reviewed for the tumor number and size, tumor grade, vascular invasion, and microscopic margins. Specimens of lymph node and/or distant metastasis were also reviewed pathologically when they were excised.

Table 1. Characteristics of all patients

Characteristics (n = 32)	Patients, n (%)
Age, years, median (range)	63.0 (49–71)
Sex, male/female	30/2
Status of extrahepatic metastases	
N1, M0	14
N0, M1	16
N1, M1	2
TNM classification[a]	
Stage IVa	14
Stage IVb	18
ICG R15, %, median (range)	11.2 (6.5–15.2)
Child-Pugh classification	
A	28
B	4
HBs-Ag positive/negative	14/18
HCV positive/negative	9/23
Total bilirubin, mg/dL, median (range)	0.75 (0.6–1.01)
Serum AFP, ng/mL, median (range)	246.5 (20.5–7876)
Serum PIVKAII, mAU/mL, median (range)	2,538.5 (555–10,939.3)
Prothrombin time, %, median (range)	89.2 (78.1–99.5)
Platelet count $\times 10^9$/L, median (range)	20.9 (15.6–26.7)
Preoperative diagnosis	
Intrahepatic maximal tumor size, mm, median (range)	85 (65–110)
<100	19 (59.4)
100≤	13 (40.6)
Intrahepatic tumor numbers	
≤2	13 (40.6)
3≤	19 (59.4)
Severe vascular invasion (sVp3/4 or sVv3)	
Yes	15 (46.9)
No	17 (53.1)

N0, no regional lymph node metastasis; N1, regional lymph node metastasis; M0, no distant metastasis; M1, distant metastasis; TNM, tumor-node-metastasis; ICGR15, indocyanine green retention rate at 15 min; HBs-Ag, hepatitis B surface antigen; HCV, hepatitis C virus; AFP, alpha-fetoprotein; PIVKAII, protein induced by vitamin K absence or antagonist II; sVp3/4, surgical first branch or main portal vein tumor thrombus; sVv3, surgical inferior vena cava tumor thrombus. [a] American Joint Committee on Cancer tumor-node-metastasis, 7th edition.

Statistical Analysis

The OS rates were calculated using the Kaplan-Meier method. The statistical significance of differences in the OS rate was examined using the log-rank test for univariate analysis. p values <0.050 were statistically significant, and variables with p values <0.100 were then entered into a multivariate analysis using the Cox proportional hazards model. Data with a normal distribution were reported as mean (standard deviation). Variables not fitting the normal distribution were presented as median (range). Continuous variables were compared by using Student's t test if normally distributed; otherwise, the Mann-Whitney U test was used. Categorical variables were compared by using the χ^2 test. Statistical analyses were performed using the JMP 14 statistical package (SAS Institute, Cary, NC, USA).

Results

Baseline Characteristics

Patient demographics and tumor features of all the 32 patients are summarized in Table 1. Of the 32 patients, 14 had lymph node metastasis only, 16 had distant metastasis only, and 2 had both lymph node and distant metastases during preoperative diagnosis (stage IVa: 14, stage IVb: 18). Twenty-eight patients had Child-Pugh grade A disease, whereas the remaining 4 patients had grade B disease. The median total bilirubin score was 0.75 (range, 0.6–1.01), and the platelet count was 20.9 (range, 15.6–26.7). According to preoperative diagnosis, 19 had tu-

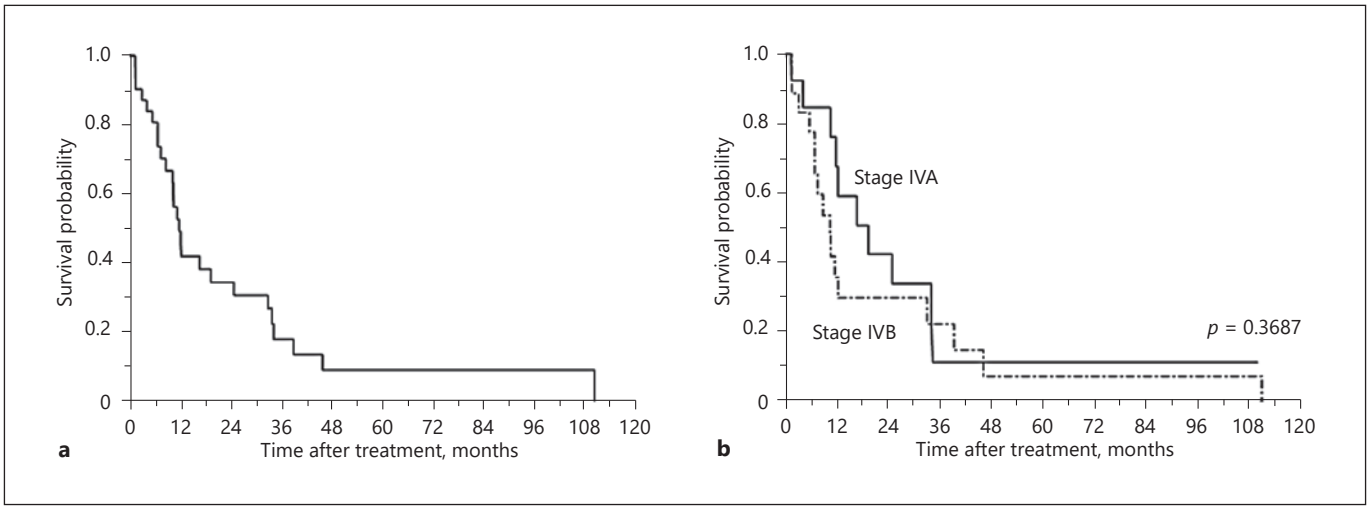

Fig. 1. a OS of all 32 patients. **b** OS according to the tumor-node-metastasis stage. OS, overall survival.

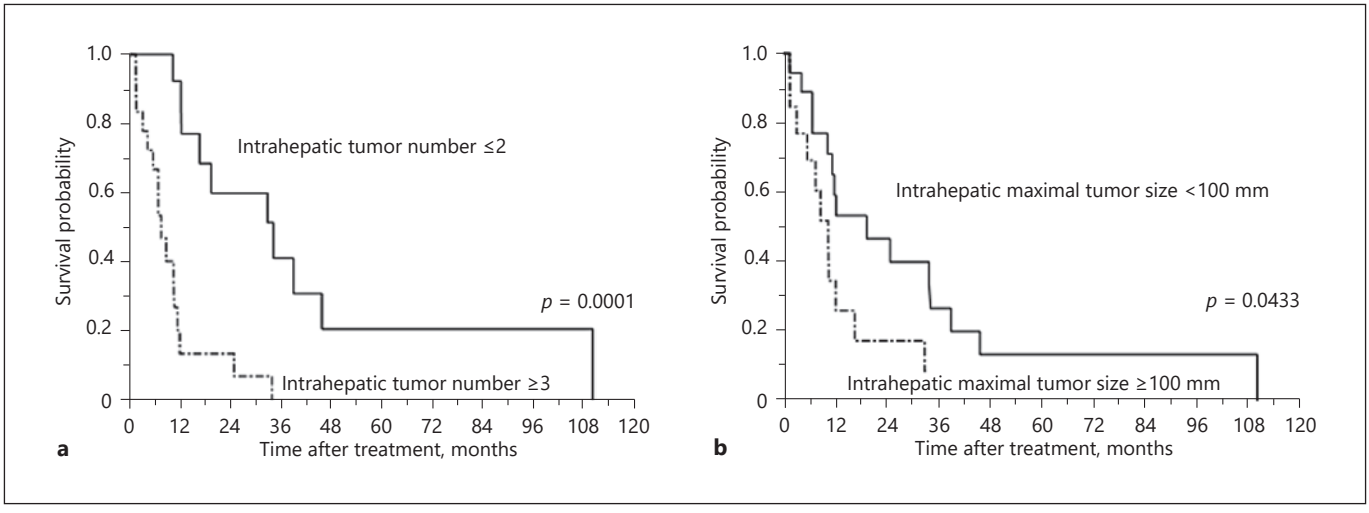

Fig. 2. a OS according to the intrahepatic tumor number. **b** OS according to the intrahepatic maximal tumor size. OS, overall survival.

mors with a maximal tumor size <100 mm, whereas the remaining 13 had tumors with a maximal tumor size ≥100 mm. Thirteen patients had ≤2 intrahepatic tumors, and the remaining 19 had ≥3 tumors. Fifteen patients (46.9%) had severe vascular invasion of more than Vp3/4 (tumor thrombus in the first branch or the main trunk) and/or Vv3 (tumor thrombus in the inferior vena cava). The median follow-up time of all patients was 10.9 months, ranging from 1.3 to 110.4 months.

Prognostic Factors for OS Rates

The OS rate of all 32 patients is shown in Figure 1a. The 3-year OS rate was 17.9%, and the median survival time (MST) was 11.8 months. The OS rates according to the TNM stage are shown in Figure 1b. There was no significant difference in the OS rates between patients with stage IVa tumors and those with stage IVb tumors (p = 0.3687). Table 2 shows the clinical and histopathological characteristics of all the patients. Univariate analysis revealed that intrahepatic maximal tumor size, intrahepatic tumor number, and residual tumors in the liver after hepatectomy were significant factors influencing OS (p < 0.05). Multivariate analyses revealed that the independent risk factors for OS were intrahepatic maximal tumor size and intrahepatic tumor number (p < 0.05; Table 2). The OS rate of all 32 patients according to intrahepatic

Table 2. Univariate and multivariate analysis of prognostic factors for OS

Factor	Patients, *n* (%)	Median survival time, months	OS rate at 3 years, %	Univariate *p* value	Multivariate *p* value (HR, 95% CI)
Age, years				0.0516	0.4362 (1.466, 0.556–3.872)
<60	14 (43.8)	10.3	10.7		
≤60	18 (56.2)	19.3	25.0		
HBs-Ag infection				0.5770	
Positive	14 (43.8)	10.5	13.4		
Negative	18 (56.2)	12.1	21.2		
HCV infection				0.5360	
Positive	9 (28.1)	19.3	31.3		
Negative	23 (71.9)	11.8	14.0		
TNM classification[a]				0.3687	
Stage IVa	14 (43.8)	19.3	11.3		
Stage IVb	18 (56.2)	10.2	22.4		
Child-Pugh classification				0.3919	
A5	22 (68.8)	12.1	10.1		
A6 and B	10 (31.2)	10.4	46.7		
Serum AFP, ng/mL				0.4562	
<100	13 (40.6)	16.6	16.8		
100≤	19 (59.4)	8.6	19.3		
Serum PIVKAII, mAU/mL				0.2263	
<2,000	14 (43.8)	16.6	21.0		
2,000≤	18 (56.2)	10.2	14.4		
Intrahepatic maximal tumor size, mm				0.0433	0.0461 (2.773, 1.018–7.980)
<100	19 (59.4)	19.3	26.7		
100≤	13 (40.6)	10.4	8.7		
Intrahepatic tumor number				0.0001	0.0017 (6.665, 2.0475–23.2530)
≤2	13 (40.6)	34.2	41.0		
3≤	19 (59.4)	7.4	0		
Severe vascular invasion (sVp3/4 or sVv3)				0.4098	
Yes	15 (46.9)	10.4	14.3		
No	17 (53.1)	12.2	21.1		
Pathological grade				0.6990	
Moderate	20 (62.5)	12.1	24.2		
Poorly	12 (37.5)	11.3	9.3		
Residual tumors in the liver after hepatectomy				0.0017	0.8721 (1.093, 0.3726–3.3519)
Yes, R (+)	12 (37.5)	8.6	0		
No, R (–)	20 (62.5)	19.3	29		

OS, overall survival; HR, hazard ratio; 95% CI, 95% confidence interval; HBs-Ag, hepatitis B surface antigen; HCV, hepatitis C virus; TNM, tumor-node-metastasis; AFP, alpha-fetoprotein; PIVKAII, protein induced by vitamin K absence or antagonist II; sVp3/4, surgical first branch or main portal vein tumor thrombus; sVv3, surgical inferior vena cava tumor thrombus. [a] American Joint Committee on Cancer tumor-node-metastasis, 7th edition.

tumor number is shown in Figure 2a. The OS rate of patients with ≤2 intrahepatic tumors was significantly better than that of patients with ≥3 tumors ($p < 0.0001$). Limited subgroup analyses of patients with stage IVa tumors and those with stage IVb tumors showed the same outcomes that the OS rates of patients with ≤2 intrahepatic tumors were significantly better than those of patients with ≥3 intrahepatic tumors (data not shown). The MST of patients with lymph node and/or distant metastases with ≤2 intrahepatic tumors was 34.2 months, whereas it was 7.4 months for patients with ≥3 intrahepatic tumors, with a significant difference. The 3-year OS rates of patients with ≤2 intrahepatic tumors was 41.0% (Fig. 2a).

The OS rates of all the 32 patients according to the intrahepatic maximal tumor size are shown in Figure 2b. The MST of patients with lymph node and/or distant me-

Table 3. Clinical details of 16 patients with LN metastases

Age, sex	Child-Pugh grade	Intrahepatic tumor numbers	Maximal tumor size, mm	Residual tumor in liver after Hx?	Features of LN metastases	Treatment for LN metastases	Status survival time, months
45, M	A (5)	1	40	R (–)	Hilar, solitary	Resection	Dead, 12.2
63, M	B (7)	1	107	R (–)	Hilar, solitary	Resection	Alive, 28.6
73, F	B (8)	1	70	R (–)	Hilar, multiple	Resection	Alive, 109.6
63, M	A (5)	2	30	R (–)	Para aorta, solitary	Resection	Dead, 34.2
73, M	A (5)	2	60	R (–)	Hilar, solitary	Resection	Dead, 19.3
77, M	A (5)	2	100	R (+)	Hilar, multiple	Resection	Dead, 16.8
56, M	A (5)	3	72	R (+)	Hilar, solitary	Resection	Dead, 24.8
63, M	A (5)	4	14	R (–)	Hilar, solitary	Resection	Dead, 11.8
69, M	B (7)	4	70	R (–)	Many, multiple	Resection	Dead, 4.1
60, M	A (5)	6	57	R (–)	Hilar, solitary	Resection	Dead, 33.9
58, M	A (5)	8	110	R (+)	Hilar, multiple	None	Dead, 10.5
49, M	A (5)	>10	110	R (–)	Hilar, solitary	Resection	Dead, 5.5
63, M	B (7)	>10	100	R (+)	Hilar, multiple	None	Dead, 1.4
72, M	A (5)	>10	52	R (–)	Hilar, multiple	Resection	Alive, 1.3
73, M	A (5)	>10	70	R (+)	Para aorta, solitary	Resection	Dead, 1.4
80, M	A (6)	>10	185	R (+)	Hilar, solitary	Resection	Dead, 6.2

Hx, hepatectomy; LN, lymph node.

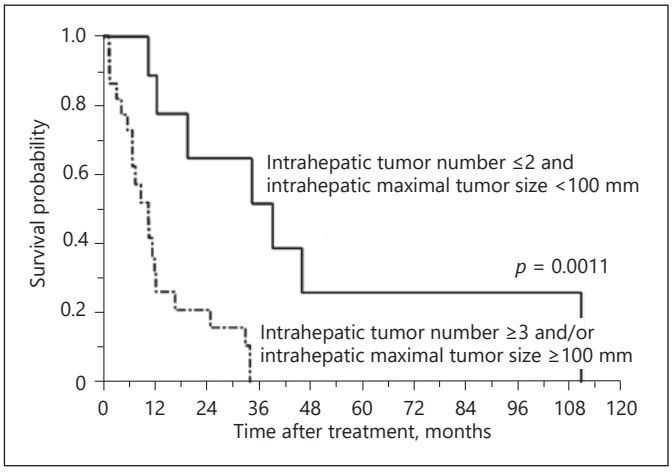

Fig. 3. OS according to the tumor status including intrahepatic tumor number and intrahepatic maximal tumor size. OS, overall survival.

tastasis with intrahepatic maximal tumor size <100 mm was 19.3 months, whereas it was 10.4 months for those with tumor size ≥100 mm ($p = 0.0433$). The 3-year OS rate of patients with intrahepatic maximal tumor size <100 mm was 26.7% (Fig. 2b).

A total of 9 patients had ≤2 intrahepatic tumors that were <100 mm considering the intrahepatic maximal tumor size. The MST of this patient population ($n = 9$) was 39.0 months, and the 3-year and 5-year OS rates were 51.9 and 25.9%, respectively (Fig. 3). Significantly better OS was observed for this patient population. Other patient and tumor factors, including viral infection status, TNM classification, Child-Pugh classification, serum AFP and PIVKAII level, vascular invasion, and pathological grade, had no influence on survival (Table 2).

Outcomes with Lymph Node Metastasis

Table 3 summarizes the details of the 16 patients with lymph node metastasis. Two patients had distant metastasis simultaneously; 14 patients were preoperatively diagnosed with stage IVa tumors, whereas 2 had stage IVb tumors. Among the 16 patients, 14 underwent lymph node dissection simultaneously with hepatectomy. Of the 14 patients, 11 were diagnosed with confirmed pathological lymph node metastasis of HCC, 2 were diagnosed with no malignancy, and pathological diagnosis was not performed for the remaining 1 patient. Of the 16 patients, 10 had solitary lymph node metastasis and the remaining 6 had multiple lymph node metastasis. The lymph node metastases were in the hilar region in 13 patients, in the para-aortic region in 2, and at multiple regions in 1. On preoperative diagnosis, 6 patients had ≤2 intrahepatic tumors, whereas the remaining 10 had ≥3 intrahepatic tumors. Six patients had apparent residual tumors within the liver after hepatectomy, whereas the remaining 10 underwent hepatectomy without apparent intrahepatic residual tumors. Of the 6 patients with residual tumors

Table 4. Clinical details of 18 patients with distant metastases

Age, sex	Child-Pugh grade	Intrahepatic tumor numbers	Maximal tumor size, mm	Residual tumor in liver after Hx?	Location of distant metastases	Treatment for distant metastases	Status survival time, months
55, M	A (5)	1	70	R (−)	Lung, multiple	Sorafenib	Dead, 10.2
47, M	A (5)	1	100	R (−)	Bone, solitary	Radiation	Dead, 12.1
64, M	A (5)	1	140	R (−)	Lung, solitary	None	Dead, 32.8
64, M	A (6)	1	60	R (−)	Lung, multiple	Sorafenib	Dead, 45.8
80, M	A (5)	1	93	R (−)	Bone, solitary	Radiation	Dead, 110.4
50, M	A (6)	2	86	R (−)	Lung, multiple	Sorafenib	Dead, 12.9
37, F	A (5)	2	76	R (−)	Peritoneum, multiple	Resection, sorafenib	Dead, 39.0
52, M	A (5)	3	63	R (−)	Lung, solitary	Sorafenib	Dead, 6.7
79, M	A (5)	6	60	R (−)	Bone, multiple	None	Dead, 6.1
49, M	A (5)	>10	130	R (+)	Lung, solitary	None	Dead, 1.4
73, M	A (5)	>10	70	R (+)	Bone, multiple	None	Dead, 1.4
63, M	A (6)	>10	200	R (+)	Lung, multiple	None	Dead, 3.0
49, M	A (5)	>10	110	R (−)	Many, multiple	Sorafenib	Dead, 5.5
49, M	A (5)	>10	90	R (+)	Adrenal grand, solitary	Resection	Dead, 6.7
37, M	B (7)	>10	220	R (−)	Lung, solitary	Sorafenib	Dead, 7.4
42, M	A (5)	>10	176	R (+)	Peritoneum, solitary	Resection	Dead, 8.6
54, M	A (6)	>10	200	R (+)	Lung, multiple	None	Dead, 10.4
65, M	A (5)	>10	74	R (+)	Bone, solitary	Radiation	Dead, 11.3

Hx, hepatectomy.

within the liver, 1 received PIHP, 4 underwent TACE, and the remaining 1 patient did not receive further treatments.

All 6 patients with ≤2 intrahepatic tumors survived for >1 year. In addition, 3 of the 6 patients had severe vascular invasion (pathological Vp3/4 or Vv3).

Outcomes with Distant Metastasis

Table 4 summarizes the details of 18 patients with distant metastasis (stage IVb). The median age was 53 years (range, 48–64 years), and 17 patients (94.4%) were men. The median score of the indocyanine green retention rate at 15 min was 8.0% (range, 5.8–13.0%); 17 patients (94.4%) had Child-Pugh grade A disease, whereas 1 (5.6%) had grade B disease. On preoperative diagnosis, the median intrahepatic maximal tumor size was 92 mm (range, 70–136 mm); 7 patients (38.9%) had ≤2 intrahepatic tumors, whereas the remaining 11 patients had ≥3 intrahepatic tumors. Hepatectomy without any apparent residual intrahepatic tumors was performed in 11 patients, whereas the remaining 7 patients underwent hepatectomy with apparent residual tumors in the liver. Of the 7 patients with residual tumors within the liver, 3 received PIHP, 1 underwent TACE, and the remaining 3 patients did not receive further treatments. The location of distant metastasis was the lungs in 9 patients, bones in 5, peritoneum in 2, adrenal grand in 1, and multiple regions in 1. Resection of the distant metastasis was performed in 3 patients (2 had peritoneal metastasis and 1 had adrenal grand metastasis). For treating distant metastases, 7 patients received sorafenib treatment after hepatectomy, 3 underwent radiation therapy, and 6 did not receive additional treatment. Two patients died <3 months after hepatectomy. Of the 7 patients who had ≤2 intrahepatic tumors, 6 survived more than 1 year. Meanwhile, all 11 patients who had ≥3 intrahepatic tumors died within 1 year.

Discussion

Despite recent advances in diagnostic techniques and therapeutic procedures, the prognosis for HCC patients with extrahepatic metastases remains poor, with a median survival of <4 months without treatment [9]. HCC with lymph node or distant metastasis is considered to be a far-advanced tumor stage, and chemotherapy is the only recommended treatment option based on several guidelines; surgical indications have rarely been discussed [9, 10]. The procedure for detecting metastasis at the time of diagnosis has not been standardized, and very little is known about the prognostic effect of metastasis on HCC patients, as independent reports have shown that the

cause of death in HCC patients with metastasis was mainly intrahepatic tumors or liver failure [19, 20]. Therefore, local control of intrahepatic tumors might have a substantial impact on HCC patients with metastasis.

The present study demonstrated the clinical relevance of hepatectomy for HCC with lymph node and/or distant metastases, when the patient had ≤2 intrahepatic tumors. The MST of HCC patients with lymph node and/or distant metastases with ≤2 intrahepatic tumors was 34.2 months, and the 3-year OS rate was 41.0%. The sub-analyses of those with lymph node (stage IVa) or distant metastasis (stage IVb) showed similar outcomes, suggesting that this patient population can be considered for hepatectomy. Among HCC patients with lymph node or distant metastasis with ≤2 intrahepatic tumors, all patients, except 1, survived more than 1 year. In contrast, all patients with ≥3 intrahepatic tumors died within 1 year.

Intrahepatic maximal tumor size was also an important factor for OS (Table 2; Fig. 2b). The MST of the patients with intrahepatic maximal tumor size <100 mm was significantly better than that of patients with intrahepatic maximal tumor size >100 mm (19.3 vs. 10.4 months). Accordingly, the MST of 9 patients with intrahepatic maximal tumor size <100 mm and ≤2 intrahepatic tumors was 39.0 months, and the 3- and 5-year OS rates were 51.9 and 25.9%, respectively. This patient population had significantly better OS; hence, hepatectomy can be considered an acceptable treatment.

Sorafenib has been the only recommended treatment option, and more recently, a novel multikinase inhibitor, lenvatinib, was validated to treat patients with advanced HCC with lymph node and/or distant metastases [21]. The REFLECT trail, a randomized control trial that indicated the non-inferiority of lenvatinib over sorafenib, demonstrated that the proportion of fatal adverse events associated with these systemic therapies was around 2% and that the proportion of serious treatment-related adverse events was around 10–18% [21]. In the present study, 3 patients (9.3%) died after <3 months; thus, the serious complications regarding the treatments seemed higher for patients undergoing hepatectomy than for those treated with systemic therapy. Considering the invasiveness of surgical intervention, this was quite obvious. Regarding the long-term outcome, the reported MST after treatment with these multikinase inhibitors was 10–14 months [10, 21], and the MST of all patients in the present study was 11.8 months. However, owing to the heterogeneity of patient backgrounds, our results cannot be directly compared with these data. In addition, in our study, of the 32 patients, 15 (46.9%) had severe vascular invasion (Vp3–4 and/or Vv3). Such cases were considered oncologic emergencies, but few other institutes consider the surgical indication for these patients when they have lymph node and/or distant metastasis because of the expected extremely poor prognosis. However, hepatectomy may have a substantial survival impact even for patients with severe vascular invasion. Meanwhile, 3 patients died <3 months after hepatectomy, and the aggressive strategy may have shortened the patients' survival. After surgical intervention, deteriorated liver function [22] and a weakened immune system [23, 24] are significant risk factors for worse survival. All 3 patients who died had >10 intrahepatic tumors; hence, the indications for hepatectomy must be cautiously determined.

Although there is no definitive conclusion regarding the surgical indications for HCC with lymph node and/or distant metastases, some patients do have a survival benefit by controlling intrahepatic HCC. Although all intrahepatic tumors can be controlled by hepatectomy, hepatectomy is not recommended for HCC patients with ≥3 intrahepatic tumors and/or intrahepatic maximal tumor size >100 mm. Meanwhile, an aggressive surgical approach may be justified for HCC patients with ≤2 intrahepatic tumors and intrahepatic maximal tumor size <100 mm, irrespective of the extent of vascular invasion.

In conclusion, the results of the present study provide information about the surgical indications for HCC patients with lymph node and/or distant metastases. Although a well-designed, randomized controlled trial with a large sample size would be preferred, our findings have substantial impact for HCC patients with extrahepatic metastases, considering the difficulty in designing such a study owing to the heterogeneity in the patient population.

Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study. This article does not contain any studies with animals performed by any of the authors.

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The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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Authors Contributions

Study conception and design: Komatsu S. Acquisition of data: Tsugawa D., Awazu M., Gon H., Yanagimoto H., Toyama H. Analysis and interpretation of data: Kido M., Tanaka M., Kuramitsu K. Drafting of manuscript: Komatsu S. Critical revision of manuscript: Fukumoto T.

References

1 El-Serag HB, Mason AC. Rising incidence of hepatocellular carcinoma in the United States. N Engl J Med. 1999;340(10):745–50.
2 Llovet JM, Bustamante J, Castells A, Vilana R, Ayuso MC, Sala M, et al. Natural history of untreated nonsurgical hepatocellular carcinoma: rationale for the design and evaluation of therapeutic trials. Hepatology. 1999; 29(1):62–7.
3 Kokudo T, Hasegawa K, Yamamoto S, Shindoh J, Takemura N, Aoki T, et al. Surgical treatment of hepatocellular carcinoma associated with hepatic vein tumor thrombosis. J Hepatol. 2014;61(3):583–8.
4 Thomas MB, Jaffe D, Choti MM, Belghiti J, Curley S, Fong Y, et al. Hepatocellular carcinoma: consensus recommendations of the National Cancer Institute Clinical Trials Planning Meeting. J Clin Oncol. 2010; 28(25):3994–005.
5 Kokudo T, Hasegawa K, Matsuyama Y, Takayama T, Izumi N, Kadoya M, et al. Survival benefit of liver resection for hepatocellular carcinoma associated with portal vein invasion. J Hepatol. 2016;65(5):938–43.
6 Nakazawa T, Adachi S, Kitano M, Isobe Y, Kokubu S, Hidaka H, et al. Potential prognostic benefits of radiotherapy as an initial treatment for patients with unresectable advanced hepatocellular carcinoma with invasion to intrahepatic large vessels. Oncology. 2007; 73(1–2):90–7.
7 Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol. 2010;17(6):1471–4.
8 Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19(3):329–38.
9 Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, et al. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009;10(1):25–34.
10 Llovet JM, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378–90.
11 Uenishi T, Hirohashi K, Shuto T, Kubo S, Tanaka H, Sakata C, et al. The clinical significance of lymph node metastases in patients undergoing surgery for hepatocellular carcinoma. Surg Today. 2000;30(10):892–5.
12 Sun HC, Zhuang PY, Qin LX, Ye QH, Wang L, Ren N, et al. Incidence and prognostic values of lymph node metastasis in operable hepatocellular carcinoma and evaluation of routine complete lymphadenectomy. J Surg Oncol. 2007;96(1):37–45.
13 Hasegawa K, Makuuchi M, Kokudo N, Izumi N, Ichida T, Kudo M, et al. Impact of histologically confirmed lymph node metastases on patient survival after surgical resection for hepatocellular carcinoma: report of a Japanese nationwide survey. Ann Surg. 2014; 259(1):166–70.
14 Ku Y, Iwasaki T, Fukumoto T, Tominaga M, Muramatsu S, Kusunoki N, et al. Induction of long-term remission in advanced hepatocellular carcinoma with percutaneous isolated liver chemoperfusion. Ann Surg. 1998; 227(4):519–26.
15 Ku Y, Iwasaki T, Tominaga M, Fukumoto T, Takahashi T, Kido M, et al. Reductive surgery plus percutaneous isolated hepatic perfusion for multiple advanced hepatocellular carcinoma. Ann Surg. 2004;239(1):53–60.
16 Fukumoto T, Tominaga M, Kido M, Takebe A, Tanaka M, Kuramitsu K, et al. Long-term outcomes and prognostic factors with reductive hepatectomy and sequential percutaneous isolated hepatic perfusion for multiple bilobar hepatocellular carcinoma. Ann Surg Oncol. 2014;21(3):971–8.
17 Komatsu S, Kido M, Tanaka M, Kuramitsu K, Tsugawa D, Awazu M, et al. Clinical relevance of reductive hepatectomy for barcelona clinic liver cancer stages B and C advanced hepatocellular carcinoma: a single-center experience of 102 patients. World J Surg. 2019; 43(10):2571–8.
18 Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004; 240(2):205–13.
19 Uka K, Aikata H, Takaki S, Shirakawa H, Jeong SC, Yamashina K, et al. Clinical features and prognosis of patients with extrahepatic metastases from hepatocellular carcinoma. World J Gastroenterol. 2007;13(3):414–20.
20 Natsuizaka M, Omura T, Akaike T, Kuwata Y, Yamazaki K, Sato T, et al. Clinical features of hepatocellular carcinoma with extrahepatic metastases. J Gastroenterol Hepatol. 2005; 20(11):1781–7.
21 Kudo M, Finn RS, Qin S, Han KH, Ikeda K, Piscaglia F, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. Lancet. 2018;391(10126):1163–73.
22 Lafaro K, Buettner S, Maqsood H, Wagner D, Bagante F, Spolverato G, et al. Defining post hepatectomy liver insufficiency: where do we stand? J Gastrointest Surg. 2015;19(11):2079–92.
23 Park SK, Brody JI, Wallace HA, Blakemore WS. Immunosuppressive effect of surgery. Lancet. 1971;1(7689):53–5.
24 Minagawa M, Oya H, Yamamoto S, Shimizu T, Bannai M, Kawamura H, et al. Intensive expansion of natural killer T cells in the early phase of hepatocyte regeneration after partial hepatectomy in mice and its association with sympathetic nerve activation. Hepatology. 2000;31(4):907–15.