Hepatic resection versus operative microwave ablation for single hepatocellular carcinoma ≤5 cm: A propensity score-matched analysis

Tomoki Ryu, MD*, Yuko Takami, MD, PhD, Yoshiyuki Wada, MD, PhD, Takanobu Hara, MD, PhD, Shin Sasaki, MD, Hideki Saitsu, MD, PhD

Department of Hepato-Biliary-Pancreatic Surgery, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan

ARTICLE INFO

ABSTRACT

Background: Little evidence exists regarding the perioperative and oncologic benefits of microwave ablation for hepatocellular carcinoma. The aim of this study was to compare the efficacy of hepatic resection and operative microwave ablation (microwave coagulo-necrotic therapy) for single hepatocellular carcinoma ≤5 cm.
Methods: Between 1994 and 2015, a total of 551 patients with a single hepatocellular carcinoma ≤5 cm were treated in our institution (hepatic resection: *n* = 128; microwave coagulo-necrotic therapy: *n* = 423). We compared overall survival and recurrence-free survival between hepatic resection and microwave coagulo-necrotic therapy. Propensity score matching analysis identified 94 matched pairs of patients to compare outcomes.
Results: After propensity score matching, baseline variables, including liver function and tumor size, were well-balanced between the 2 groups. The 5- and 10-year overall survival rates were 76% and 47% for hepatic resection and 77% and 48% for microwave coagulo-necrotic therapy, respectively (*P* = .865). The 5- and 10-year recurrence-free survival rates were 55% and 41% for hepatic resection and 47% and 32% for microwave coagulo-necrotic therapy, respectively (*P* = .377). In the subgroup analysis, the hepatic resection group had better recurrence-free survival than the microwave coagulo-necrotic therapy group in patients with tumor size >3 cm, with 5-year recurrence-free survival rates of 56.5% and 32.4% in the hepatic resection and microwave coagulo-necrotic therapy group, respectively (*P* = .029).
Conclusion: Our propensity score matching study confirmed no statistically significant differences in both overall survival and recurrence-free survival between hepatic resection and microwave coagulo-necrotic therapy for single hepatocellular carcinoma ≤5 cm; however, hepatic resection is recommended for hepatocellular carcinoma with tumor size >3 cm when patients have good liver function.

© 2019 Elsevier Inc. All rights reserved.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third leading cause of cancer-related death.[1] HCC often occurs in patients with chronic hepatitis or liver cirrhosis secondary to hepatitis C virus or hepatitis B virus infection.[2] With recently improved screening and surveillance in patients with chronic liver disease, the number of patients with HCC diagnosed at an early-stage has increased[3] because HCC ≤5 cm with no macroscopic vascular invasion is considered early-stage and is classified as T1-stage HCC in the tumor-node-metastasis (TNM) classification developed by the American Joint Committee on Cancer and the Union for International Cancer Control.[4] According to the management guidelines of the European Association for the Study of the Liver and the American Association for the Study of Liver Diseases, the recommended treatment modalities for T1-stage HCC include hepatic resection (HR), local ablation, and liver transplantation.[5,6] In some countries with a shortage of donors for liver transplantation, HR or local ablation is the main curative treatment option for T1-stage HCC.

HR is generally considered to be a standard treatment for patients with T1-stage HCC,[7] whereas local ablation therapy, such as radiofrequency ablation (RFA) and microwave ablation, is used widely a therapeutic strategy for smaller (≤5 cm) HCC or in patients with impaired liver function.[8–10] Microwave ablation has attracted recent attention as a local ablative therapy for HCC in both Asia and western countries.[10,11] We have performed operative microwave

* Reprint requests: Tomoki Ryu, MD, Department of Hepato-Biliary-Pancreatic Surgery, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, 1-8-1 Jigyohama Chuo-ku, Fukuoka 810-8563, Japan.
E-mail address: ryu.tomoki.mq@mail.hosp.go.jp (T. Ryu).

ablation, termed microwave coagulo-necrotic therapy (MCN), for HCC for >20 years and reported its feasibility and safety for HCC patients previously.[12–14] Our previous studies revealed no differences in long-term outcomes between HR and MCN for HCC patients with tumors ≤3 cm and with 3 lesions or lesions within the Milan criteria.[12,13] These retrospective trials, however, were not case-matched or randomized clinical studies, and the results were potentially influenced by selection bias. Therefore, the true oncologic benefits of MCN for HCC remain to be established.

In the present study, our aim was to investigate the perioperative and long-term outcomes of HR and MCN for single HCC ≤5 cm, using propensity score matching (PSM) to minimize potential confounding bias at patient backgrounds.

Methods

Patients

We analyzed retrospective patient data from a computerized database that recorded all relevant preoperative and postoperative information. From July 1994 to December 2015, 1,232 patients underwent hepatic surgery including HR and MCN, for primary HCC in the Department of Hepato-Biliary-Pancreatic Surgery at Kyushu Medical Center. Among them, patients with single HCC ≤5 cm with no evidence of macroscopic vascular or bile duct invasion or and extrahepatic disease were eligible for the study. A total of 551 patients were included in this study; 128 underwent HR, and 423 underwent MCN. We used PSM to match patients in the HR and MCN groups in a 1:1 ratio. We compared perioperative outcomes, long-term outcomes (overall survival [OS], and recurrence-free survival [RFS]) and the characteristics of the first HCC recurrence in both groups.

HCC lesions in each patient were diagnosed preoperatively by ultrasonography (US), dynamic computed tomography (CT), or enhanced magnetic resonance imaging. The morphologic patterns of the tumor (regular or irregular) were defined as follows. When the tumor was round with a distinct margin and no budding portion at the periphery, the morphologic pattern was considered to be regular. In contrast, when the tumor was round with a focally protruding area or lobulated with multiple nodular lesions, the morphologic pattern was considered to be irregular. In addition, tumors were considered to be in proximity to a major vessel when the tumors were located within 10 mm of the inferior vena cava, hepatic veins, or major Glissonean branches. These radiologic findings were determined in each patient by the authors who had >15 years of experience in liver surgery and who were blinded to the patients' clinical records. The final diagnosis of HCC was confirmed by pathologic examination of resected specimens or tumor biopsy in all patients. Noncancerous liver tissue was inspected for evidence of cirrhosis, which was defined as grade 4 fibrosis according to the criteria of Desmet et al.[15] The recorded data included age, sex, hepatitis virus markers (hepatitis B virus surface antigen and hepatitis C virus antibody), blood chemistry parameters, indocyanine green retention rate at 15 min (ICG-R15), Child-Pugh classification, and 3 tumor markers: α-fetoprotein (AFP), *Lens culinaris* agglutinin-reactive fraction of AFP (AFP-L3), and des-γ-carboxy prothrombin (DCP). Serum concentrations of AFP, AFP-L3, and DCP were measured within 1 week before operation. The upper limits of the normal ranges of AFP, AFP-L3, and DCP in our institution were 20 ng/mL, 10%, and 40 mAU/mL, respectively. Tumor marker levels greater than the upper normal range were defined as positive markers for HCC. Patients were classified according to the number of positive tumor markers as negative, single-positive, double-positive, or triple-positive.[13] This study was conducted in accordance with the Declaration of Helsinki and the

ethical guidelines for clinical studies of the Ministry of Health, Labour and Welfare in Japan. The study protocol was approved by the Ethics Committee on Clinical Investigations of Kyushu Medical Center (Approval No. 18C161).

Treatment

HR and MCN were performed by the same surgical team of dedicated liver surgeons led by at least one consultant specialist. The treatment approach was decided at multidisciplinary HCC team meetings after considering the liver function, tumor location, and extent of tumor spread of each individual patient. MCN was considered preferentially to treat patients with HCC ≤ 3 cm, whereas HR was performed in patients with good liver function or tumors located in areas suitable for resection (ie, surface or edge of the liver). HR was considered the first-choice treatment for patients with HCC > 3 cm, although MCN was also selected for some patients with impaired liver function, older age, poor performance status, or who declined HR.

In the HR group, the extent of resection was determined based on the tumor extent and hepatic reserve assessed by the Child-Pugh score and the criteria established by Makuuchi et al.[16] Anatomic hepatic resection procedures were defined based on the Brisbane 2000 classification.[17] Right subcostal or upper midline incisions were used according to tumor location. After intra-operative US examination to confirm tumor location and size, liver parenchymal dissection was performed with an ultrasonic surgical aspirator or clamp-crushing method under an intermittent Pringle maneuver. During parenchymal dissection, attempts were made to achieve a resection margin of at least 1 cm.

MCN procedures were performed according to our standardized methods as reported previously.[12–14] We performed MCN as an open approach via a laparotomy, thoracotomy, or laparoscopy; we used US routinely in all patients to identify lesions and monitor treatment effect. Using a 2,450-MHz system microwave generator (Alfresa Pharma, Osaka, Japan), the ablation power settings and duration were either a single coagulation at 60 to 65 W for 60 s per pulse using a 16-gauge, 150-mm-long needle or at 80 to 85 W for 30 s per pulse using a 21-gauge, short needle (range, 10–30 mm). The type of needle was selected based on the particular tumor conditions. When the tumor was located deeper in the liver, a long-needle electrode was inserted under US guidance, and when the tumor was located on the surface of the liver, we used a short-needle electrode of appropriate length for the tumor diameter. With each single coagulation, a necrotic area of approximately 1.0 cm in diameter was formed. MCN repeats electrode insertion and irradiation from the tumor edge to the tumor center to avoid increasing intratumoral pressure and to obtain an adequate ablation margin of 10 mm outside the tumor margin. The criteria for an open approach were as follows. When tumors located in the anterior or lateral segments of the liver (segments 2, 3, 4, and 5), we placed patients in the supine position and used a right subcostal or upper midline incision. When the tumor was located in the posterior or superior segments of the liver (segments 1, 6, 7, and 8), we operated in the left semilateral position. After making a right intercostal incision 5 to 8 cm long and a short thoracotomy, MCN was performed by passing the needle through the diaphragm. When the tumor was located on the surface of the liver, MCN was performed via laparoscopy in selected patients.

Patient follow-up

Perioperative morbidities were stratified by severity based on the Clavien-Dindo classification[18]; major complications were considered grade III or above. Treatment response was evaluated by

Table I
Comparison of the clinicopathologic characteristics in the HR and MCN groups in the unmatched and propensity score-matched cohort

Characteristic	Unmatched cohort			Propensity score-matched cohort		
	HR (n = 128)	MCN (n = 423)	P value	HR (n = 94)	MCN (n = 94)	P value
Age, y, median (range)	68 (42–85)	71 (38–87)	.018	71 (42–84)	71 (38–87)	.722
Sex, male, n (%)	90 (70%)	270 (64%)	.173	63 (67%)	65 (69%)	.681
Hepatitis B virus infection, n (%)	21 (16%)	68 (16%)	.929	15 (16%)	18 (19%)	.565
Hepatitis C virus infection, n (%)	69 (54%)	293 (69%)	.002	55 (59%)	52 (55%)	.658
Albumin, g/dL, median (range)	4.0 (2.5–5.5)	3.8 (1.8–5.1)	<.001	4.0 (2.5–5.5)	4.1 (2.4–4.9)	.908
Total bilirubin, mg/dL, median (range)	0.7 (0.3–2.3)	0.8 (0.2–2.9)	<.001	0.7 (0.4–2.3)	0.7 (0.3–2.1)	.979
Prothrombin activity, %, median (range)	90 (47–139)	82 (32–170)	<.001	90 (47–137)	88 (59–170)	.310
ICGR15, %, median (range)	18.2 (0.6–91.8)	22.9 (0.6–83.7)	.006	18.3 (0.6–65.9)	19.5 (3.1–62.9)	.546
Platelets, μL, median (range)	16.7 (4.5–45.4)	12.0 (3.0–33.0)	<.001	15.8 (4.5–45.4)	14.7 (3.0–28.6)	.138
Child-Pugh class A, n (%)	120 (94%)	351 (83%)	.001	88 (94%)	87 (93%)	.774
ALBI grade 1, n (%)	81 (63%)	181 (43%)	<.001	61 (65%)	60 (64%)	.879
Tumor Size, mm, median (range)	30.3 (10.4–50.0)	22.8 (7.9–50.0)	<.001	28.9 (10.4–50.0)	30.7 (7.9–50.0)	.949
≤30 mm, n (%)	62 (48%)	323 (76%)	<.001	51 (54%)	46 (49%)	.382
AFP, ng/mL, median (range)	10 (0.9–25,314)	15 (0.9–14,744)	.039	11 (1.1–15,468)	9.5 (2.8–14,744)	.946
AFP-L3, %, median (range)	0.5 (0–89.4)	2.4 (0–88.1)	.632	0.5 (0–89.4)	0.5 (0–88.1)	.619
DCP, mAU/mL, median (range)	43 (0–23,500)	30 (0–9,760)	.011	33 (0–12,700)	54 (0–9,760)	.544
Double- or triple-positive tumor markers, n (%)	43 (34%)	131 (31%)	.633	32 (34%)	28 (30%)	.521
Arterial phase findings on CT, high, n (%)	115 (90%)	372 (88%)	.325	78 (83%)	81 (86%)	.544
Tumor morphologic pattern, irregular, n (%)	42 (33%)	122 (29%)	.312	27 (29%)	31 (33%)	.527
Proximity to major vessel, yes, n (%)	32 (25%)	118 (28%)	.432	22 (23%)	29 (31%)	.250
Liver cirrhosis, n, (%)	37 (29%)	183 (43%)	.001	29 (31%)	34 (36%)	.388

ICGR15, indocyanine green retention rate at 15 min.

dynamic CT 1 to 2 weeks postoperatively in both groups. All patients were followed every 2 to 3 months with US and blood chemistry evaluations, including AFP, AFP-L3, and DCP. Imaging studies (dynamic CT or enhanced magnetic resonance imaging) were performed every 4 to 6 months. All patients were followed up until death or April 2018.[19] Local recurrence was defined as the presence of a recurrent tumor within 1 cm of the previously treated tumor site identified on follow-up imaging. When recurrent tumors were found, regardless of the type of recurrence, MCN or HR was again attempted based on the same criteria used to select treatment for the initial tumor; however, if MCN or HR was considered unsuitable to treat multiple recurrences, we performed transcatheter arterial chemoembolization (TACE) or hepatic arterial infusion chemotherapy. Patients with extrahepatic metastases were usually treated with sorafenib or radiation therapy.

Propensity score matching analysis

We performed PSM analysis to decrease selection bias by building a matched group of patients to compare morbidities, OS, and RFS between patients who received HR or MCN.[20] Variables entered in our propensity model were age, sex, hepatitis C virus antibody positivity, serum albumin and total bilirubin concentrations, prothrombin time, ICG-R15, serum AFP and DCP levels, and tumor size. We calculated propensity scores by applying these variables to a logistic regression model and calculated C-statistics to evaluate the goodness of fit. One-to-one PSM was performed with a caliper width ranging <0.20 of the pooled standard deviation of estimated propensity scores.

Statistical analysis

Continuous variables were presented as median (range) and compared using the Mann-Whitney U test. Categorical variables were compared using Fisher exact probability method or χ^2 tests. OS was defined as the interval from time of operation to death or the date of the last or most recent follow-up visit. RFS was defined as the interval from time of operation to the date of diagnosis of

the first recurrence or last follow-up. OS and RFS curves were calculated using the Kaplan-Meier method and compared using the log-rank test. We used a Cox proportional hazards model for univariate and multivariate analyses of the prognostic factors related to survival and recurrence. All P values were derived from 2-tailed tests. All statistical analyses were performed using JMP 12 software (SAS Institute, Inc., Cary, NC).

Results

Preoperative characteristics and postoperative outcomes in the entire cohort

Preoperative characteristics of the entire cohort are summarized in Table I. We found substantial differences in background variables between the 2 groups before PSM analysis. The HR group had a significantly younger median age and lesser percentage of patients who were positive for hepatitis C virus antibody than the MCN group. Liver function variables, such as serum albumin and total bilirubin, prothrombin time, platelet count, ICG-R15, and Child−Pugh class, were better, and histologic liver cirrhosis was less common in the HR group than the MCN group. In contrast, tumor size and serum DCP level were greater in the HR versus MCN groups. In the HR group, anatomic hepatic resection was performed in 75 patients. We encountered no treatment-related mortality in either group.

The median follow-up time for the entire study population was 65.8 months (HR group: 64.0 months, MCN group: 66.7 months; P = .658). The 1-, 3-, 5-, and 10-year OS rates were 99%, 89%, 78%, and 47%, respectively in the HR group, and 98%, 86%, 73%, and 40% in the MCN group (P = .074; Fig 1, A). The 1-, 3-, 5-, and 10-year RFS rates were 90%, 66%, 54%, and 40% in the HR group, and 92%, 57%, 41%, and 22% in the MCN group (P = .010; Fig 1, B).

Preoperative characteristics and postoperative outcomes in the PSM cohort

PSM analysis identified 94 matched pairs of patients from each treatment group. Preoperative characteristics of patients after PSM
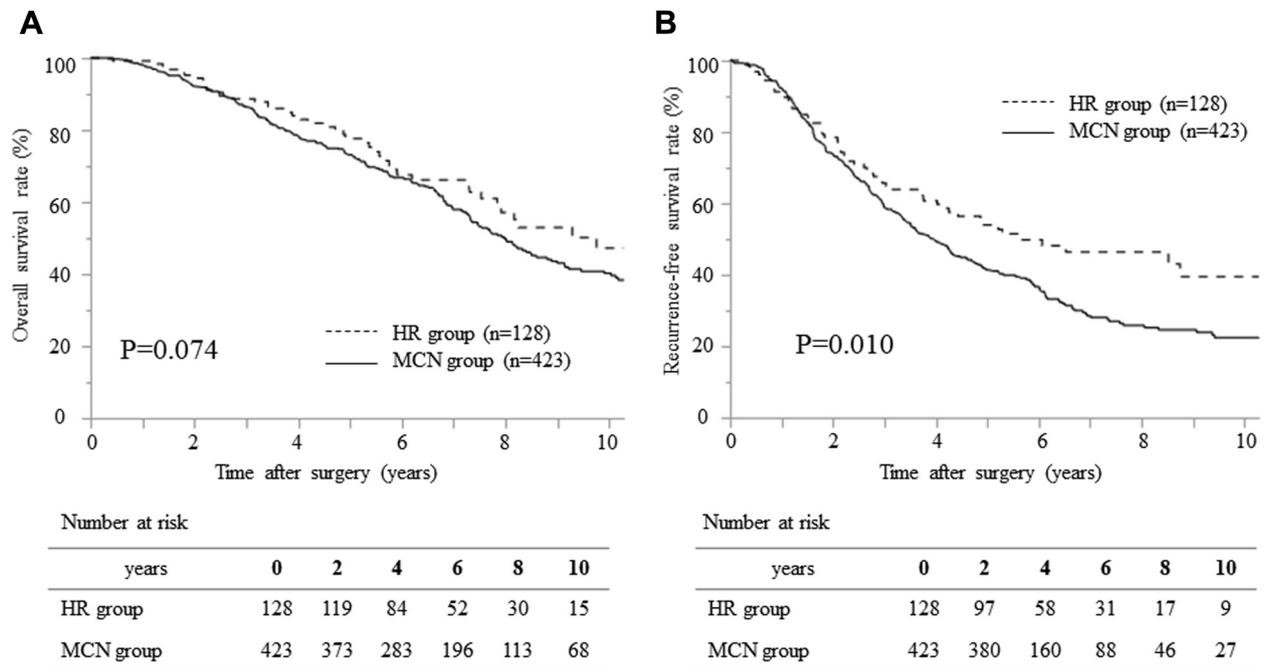
A

B

Number at risk

years	0	2	4	6	8	10
HR group	128	119	84	52	30	15
MCN group	423	373	283	196	113	68

Number at risk

years	0	2	4	6	8	10
HR group	128	97	58	31	17	9
MCN group	423	380	160	88	46	27

Fig 1. Long-term survival outcomes after HR or MCN. (*A*) Overall survival and (*B*) recurrence-free survival rates.

Table II
Perioperative characteristics of patients in the HR and MCN groups in the propensity score-matched cohort

Characteristics	HR (n = 94)	MCN (n = 94)	P value
Operating time, min, median (range)	165 (50–511)	87 (54–198)	<.001
Blood loss, g, median (range)	109 (1–1,846)	10 (1–103)	<.001
Intraoperative blood transfusion, n (%)	5 (5%)	1	.083
Morbidity, n (%)	11 (12%)	8 (9%)	.452
Intra-abdominal abscess	3 (3%)	1 (1.1%)	
Bile leakage	1	0	
Wound infection	1	1	
Ascites	1	1	
Pleural effusion	0	3 (3.4%)	
Portal thrombosis	3 (3%)	0	
Cardiac arrhythmia	0	1	
Pneumonia	1	1	
Renal disorder	1	0	
Complication of Clavien-Dindo grade IIIA or above, n (%)	5 (5%)	3 (3%)	.468
IIIA	4 (4%)	3 (3%)	
IIIB	1	0	
IV	0	0	
V	0	0	
Mortality, n (%)	0	0	—
Postoperative hospital stay, days, median (range)	12 (7–75)	10 (6–32)	<.001

analysis are presented in Table I. Matched patients in the HR and MCN groups had similar baseline characteristics, including age, cause of underlying liver disease, background liver function, tumor size, and tumor markers (all *P* > .05).

Perioperative outcomes of the HR and MCN groups in the matched cohort are summarized in Table II. In the HR group, 90 patients underwent open hepatectomy and 4 underwent laparoscopic hepatectomy. Anatomic hepatic resection was performed in 56 patients. In the MCN group, 55 patients underwent MCN via thoracotomy, 36 via laparotomy, and 3 via laparoscopy. The median operating time and median blood loss were both less (*P* < .001) in the MCN group than the HR group. In the MCN group, only one patient required intraoperative platelet transfusion because of a platelet count of 3.0×10^4 /μL secondary to severe liver cirrhosis. There were no differences in postoperative morbidity rate between

groups. Major complications were experienced by five patients (5%; 3 intra-abdominal abscesses, 1 bile leakage, and 1 wound infection) in the HR group and 3 patients (3%; 1 intra-abdominal abscess, 1 wound infection, and 1 pleural effusion) in the MCN group (*P* = .468). Clavien-Dindo grade IV or V complications did not occur in either group. The median postoperative hospital stay was less for MCN patients than HR patients.

The median follow-up time in the HR and MCN groups was 63.0 months and 58.3 months (*P* = .664). The 1-, 3-, 5-, and 10-year OS rates were 100%, 89%, 76%, and 47% in the HR group and 99%, 85%, 77%, and 48% in the MCN group (*P* = .865; Fig 2, *A*). The 1-, 3-, 5-, and 10-year RFS rates were 90%, 65%, 55%, and 41% in the HR group and 92%, 62%, 47%, and 32% in the MCN group (*P* = .377; Fig 2, *B*). There were no differences in OS or RFS between groups in the matched cohort.
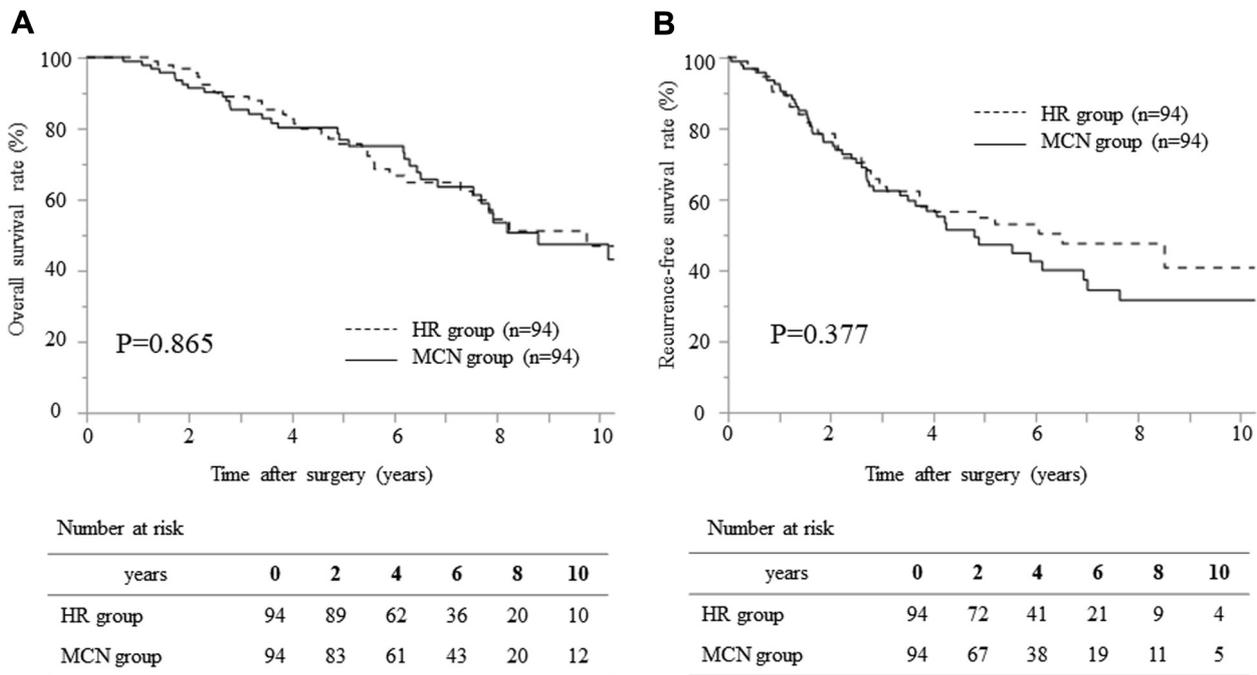
A

B

Number at risk

years	0	2	4	6	8	10
HR group	94	89	62	36	20	10
MCN group	94	83	61	43	20	12

Number at risk

years	0	2	4	6	8	10
HR group	94	72	41	21	9	4
MCN group	94	67	38	19	11	5

Fig 2. Long-term survival outcomes after HR or MCN in a propensity score-matched cohort. (*A*) Overall survival and (*B*) recurrence-free survival rates.

Table III
Recurrence characteristics of patients in the HR and MCN groups in the propensity score-matched cohort

Characteristic	HR (n = 94)	MCN (n = 94)	P value
Recurrence, *n* (%)	44 (47%)	49 (52%)	.401
Within 2-year recurrence, *n* (%)	20 (21%)	22 (23%)	.726
Intrahepatic recurrence, *n* (%)	42 (45%)	48 (51%)	.362
Maximum tumor size, mm, median (range)	20 (10–34)	19 (8–53)	.898
No. of tumors, *n* (%)			.756
Single	19 (20%)	25 (26%)	
2–3	12 (13%)	13 (14%)	
>3	11 (12%)	10 (11%)	
Extrahepatic recurrence, *n* (%)	3 (3.4%)	1 (1.1%)	.422
Local recurrence, *n* (%)	2 (2.1%)	7 (7.4%)	.088
Characteristic on recurrence occurrence			
Serum albumin, g/dL, median (range)	3.9 (2.5–4.7)	3.9 (2.4–4.9)	.808
Total bilirubin, mg/dL, median (range)	0.7 (0.3–2.1)	0.7 (0.2–2.2)	.449
Prothrombin activity, %, median (range)	87 (40–117)	88 (65–128)	.477
Platelets, µL, median (range)	14.0 (4.0–34.0)	14.4 (5.0–35.6)	.539
Child-Pugh class, A, *n* (%)	38 (40%)	39 (41%)	.393
AFP, ng/mL, median (range)	9.1 (1.5–28,300)	6.5 (1.3–6,835)	.948
AFP-L3, %, median (range)	0.5 (0–91.1)	0.5 (0–89.5)	.728
DCP, mAU/mL, median (range)	27 (13–65,400)	46 (9–11,700)	.183
Treatment for recurrence, *n* (%)			.928
Repeat hepatectomy	1 (1.1%)	1 (1.1%)	
Repeat MCN	26 (27%)	31 (33%)	
TACE	5 (5.2%)	6 (6.4%)	
HAIC	7 (7.4%)	6 (6.4%)	
Sorafenib	2 (2.1%)	0	
Radiation	1 (1.1%)	1 (1.1%)	
BSC	4 (4.3%)	4 (4.3%)	

BSC, best supportive care.

HCC recurrence and treatment of the PSM cohort

Recurrence characteristics in the HR and the MCN groups in the matched cohort are summarized in Table III. Forty-four patients (47%) in the HR group and 49 (52%) in the MCN group experienced a postoperative HCC recurrence. Early HCC recurrence rates (within 2 years postoperatively) were not different between HR and MCN groups ($P = .726$). As for the number of intrahepatic recurrences, we found no difference between groups. Extrahepatic recurrences were found in 3 patients (bone, lung, and lymph node) in the HR group and 1 patient (bone) in the MCN group ($P = .422$). Local recurrence was detected in 2 patients (2%) in the HR group and 7 patients (7%) in the MCN group ($P = .088$). Liver function parameters on recurrence and the proportions of the treatment modality for recurrences showed no differences between groups. No patients underwent salvage liver transplantation for recurrences. The 2

Table IV
Overall survival and recurrence-free survival in selected subgroups in the propensity score-matched cohort

Subgroup	n	5-year OS			5-year RFS		
		HR	MCN	*P* value	HR	MCN	*P* value
Age							
≤70 y	83	78.9	82.4	.864	55.9	49.3	.328
>70 y	105	72.5	73.6	.873	52.8	50.9	.977
Hepatitis virus infection status							
Hepatitis B virus	33	84.8	76.3	.729	71.8	51.3	.119
Hepatitis C virus	107	72.9	74.9	.876	44.7	47.1	.972
NonB-nonC	52	75.9	79.6	.406	59.6	56.0	.811
ALBI							
Grade 1	121	84.4	80.7	.535	65.2	50.9	.155
Grade 2 or 3	67	64.2	73.4	.980	34.4	41.4	.778
Maximum tumor size							
≤30 mm	97	77.6	88.7	.652	51.5	61.2	.121
>30 mm	91	73.4	69.4	.685	56.5	32.4	.029
AFP							
≤100 ng/mL	144	77.4	78.4	.695	50.8	47.9	.690
>100 ng/mL	44	68.8	71.4	.419	63.8	46.9	.411
DCP							
≤100 mAU/mL	122	77.3	88.1	.377	58.3	59.5	.969
>100 mAU/mL	66	71.0	62.1	.226	45.1	34.3	.252
No. of positive tumor marker							
Negative or single	128	79.1	85.0	.669	57.3	53.4	.926
Double or triple	60	70.9	63.8	.694	49.0	33.5	.162
Tumor morphologic pattern							
Regular	130	78.5	85.2	.566	56.6	55.4	.971
Irregular	58	73.7	65.0	.211	50.9	31.6	.064
Proximity to major vessel							
Yes	51	70.1	73.3	.973	68.2	52.5	.110
No	137	79.2	80.4	.649	50.6	45.6	.784

NonB-nonC, negative for hepatitis B surface antigen and hepatitis C antibody.

Table V
Recurrence patterns according to tumor size in the HR and MCN groups in the propensity score-matched cohort

Recurrence pattern	Primary tumor size ≤30 mm			Primary tumor size >30 mm		
	HR (n = 53)	MCN (n = 47)	*P* value	HR (n = 41)	MCN (n = 47)	*P* value
Intrahepatic recurrence, *n* (%)	24 (46%)	15 (32%)	.146	18 (44%)	33 (70%)	.009
Local recurrence	1	1	.458	1	6 (13%)	.031
Same segment	2	2 (4%)	.885	6 (15%)	8 (17%)	.730
Same lobe	9 (17%)	5 (11%)	.380	4 (10%)	10 (21%)	.073
Opposite lobe	7 (13%)	2	.114	4 (10%)	4 (9%)	.787
Bilobar	5 (9%)	5 (11%)	.813	3 (7%)	5 (11%)	.616
Extrahepatic recurrence, *n* (%)	1	0	.258	2 (5%)	1	.476

patients with local recurrence after HR underwent repeat HR and TACE for recurrent tumors, and among patients with local recurrence after MCN, 5 patients underwent repeat MCN and 2 underwent TACE.

Subgroup analyses of OS and RFS in the PSM cohort

The results of the subgroup analyses of OS and RFS in the matched cohort are summarized in Table IV. Kaplan-Meier analyses showed that there were no differences in OS between the HR and MCN groups for all subgroup analyses. Regarding RFS, there were no differences between the HR and MCN groups in all subgroup analyses except for tumor size. Kaplan-Meier analyses showed that the HR group had a better RFS than the MCN group in patients with tumor size >3 cm; the 5-year RFS rates were 56.5%, and 32.4% in the HR and MCN groups (*P* = .029). Recurrence patterns according to tumor size are summarized in Table V. In patients with tumor size ≤3 cm, 1 out of 53 patients experienced local recurrence after HR, and 1 out of 47 patients experienced local recurrence after MCN (*P* = .458). In patients with tumor size >3 cm,

1 out of 41 patients experienced local recurrence after HR, and 6 out of 47 patients (13%) experienced local recurrence after MCN (*P* = .031).

Prognostic factors for OS and RFS in the PSM cohort

We evaluated factors associated with OS and RFS using univariate and multivariate analyses in the matched cohort (Table VI). Multivariate analyses showed that an albumin-bilirubin (ALBI) grade of 2 or 3 (hazard ratio, 2.73; 95% confidence interval [95% CI], 1.69–4.74; *P* < .001) and maximal tumor size >3 cm (hazard ratio, 1.64, 95% CI, 1.01–2.69; *P* = .045) were independent risk factors for OS. Multivariate analyses also showed that ALBI grade 2 or 3 (hazard ratio, 2.13; 95% CI, 1.38–3.26; *P* < 0.001), maximal tumor size >3 cm (hazard ratio, 1.68; 95% CI, 1.08–2.64; *P* = .021), and double- or triple-positive tumor markers (hazard ratio, 1.67; 95% CI, 1.07–2.58; *P* = .025) were independent risk factors for RFS. Accordingly, MCN was not confirmed as an independent risk factor for OS or RFS.

Table VI
Univariate and multivariate analysis for overall survival and recurrence-free survival in the propensity score-matched cohort

Characteristic	Overall survival						Recurrence-free survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age, y, (>70)	1.18	0.73–1.94	.487				1.20	0.79–1.82	.381			
Sex (male)	1.07	0.64–1.89	.799				1.26	0.81–2.03	.305			
HCV-Ab (positive)	1.44	0.88–2.41	.149				1.29	0.86–1.97	.225			
ALBI (grade 2 or 3)	2.74	1.70–4.74	< .001	2.73	1.69–4.46	< .001	1.81	1.20–2.73	.005	2.13	1.38–3.26	< .001
Platelet count (x104 /µL; ≤10)	1.63	0.89–2.84	.108				1.47	0.60–1.75	.836			
ICGR15 (%; >15)	1.10	0.68–1.80	.691				1.35	0.89–2.12	.163			
Maximum tumor size (mm; >30)	1.56	0.39–1.04	.072	1.64	1.01–2.69	.045	1.86	1.23–2.82	.003	1.68	1.08–2.64	.021
AFP (ng/mL) (>100)	1.26	0.71–2.12	.415				1.01	0.63–1.69	.957			
DCP (mAU/mL) (>100)	1.51	0.91–2.47	.106				1.94	1.28–2.93	.002	1.45	0.92–2.29	.109
No. of positive tumor marker (double or triple)	1.59	0.95–2.62	.078	1.59	0.97–2.65	.058	1.67	1.08–2.55	.021	1.67	1.07–2.58	.025
Tumor morphologic pattern (irregular)	1.26	0.49–1.32	.366				1.71	1.12–2.58	.014	1.29	0.81–2.04	.279
Proximity to major vessel (yes)	1.19	0.68–1.98	.534				1.03	0.64–1.61	.898			
Surgery (MCN)	1.01	0.63–1.64	.951				1.17	0.78–1.28	.441			

HCV-Ab, hepatitis C virus antibody; *ICGR15*, indocyanine green retention rate at 15 min.

Discussion

Microwave ablation has been used as a local ablation therapy for HCC in Japan since 1988.[21–23] The numbers of retrospective cohort studies comparing microwave ablation and HR for primary HCC have been increasing worldwide. These studies report no differences between these 2 treatments with 5-year OSs after microwave ablation and HR of 43% to 67% and 38% to 72%.[24–28] A recent systematic review of nine retrospective studies comparing microwave ablation and HR revealed that microwave ablation was as effective as HR regarding OS and RFS[29]; these previous studies, however, were not case-matched or randomized clinical studies; therefore, the oncologic benefits of microwave ablation for HCC are not well established. To our knowledge, this is the first study to compare HR and microwave ablation for HCC by using a PSM analysis.

MCN, our innovative, microwave ablation procedure, was designed by Saitsu et al in 1988 and first reported in 1991.[21] Since then, we have gained experience with MCN and reported its efficacy and safety not only for HCC but also for metastatic liver tumors from other organs.[30–32] The most important concept of MCN is that it is designed to prevent intrahepatic dissemination secondary to intraoperative manipulation of the cancer cells. MCN initially irradiates tissue surrounding the tumor and then irradiates the tumor center to prevent spread of cancer cells. This aspect of our technique is the greatest difference between MCN and other percutaneous local ablative therapies, starting with puncture and ablation at the tumor center. Electrode insertion and ablation at the tumor center can scatter tumor cells through portal veins or hepatic veins because of the high intratumoral pressure during ablation.[33,34] Multiple scattered recurrences or intrahepatic dissemination after RFA have been reported in some studies.[35–37] A recent study reported that intrahepatic parenchymal pressure also increased during microwave ablation.[38] In MCN, we insert the first electrode at the tumor edge and not in the center of the tumor mass performing insertions and coagulations at 5 to 8 times, even for a tumor ≤2 cm in diameter. Although we have not monitored intratumoral pressure during MCN, we think that our procedure avoids any undesirable increases in intratumoral pressure and may explain why we have not experienced the type of recurrences seen after RFA. Another important finding of our procedure is that we can predict the ablation zone more precisely. Although our single

coagulation formed a small necrotic area of approximately 1.0 cm in diameter, repeated insertion enabled us to control the area of ablation more easily. This procedure is extremely valuable, especially for tumors near a major vessel. Taken together, we believe that our MCN procedure is oncologically appropriate and have adopted it as a first-choice procedure for small HCC.

At the initial analysis before PSM analysis, we showed that HR was associated with better RFS compared with MCN (*P* = .010), and OS rates tended to be greater in the HR group than in the MCN group (*P* = .074). This finding could be attributed to the better liver function in the HR group. The prevalence of liver cirrhosis and positive hepatitis C virus antibody in the HR group were also less than in the MCN group. Therefore, we applied a PSM analysis to minimize potential selection bias between the 2 groups. In our PSM model, all preoperative characteristics, including liver function parameters and tumor-related factors, were well matched between the 94 patients in each of the HR and the MCN groups. To investigate long-term outcomes, Kaplan–Meier analyses of OS and RFS rates showed no differences between HR and MCN (*P* = .865 and *P* = .377, respectively). The 5-year OS of 76 % after MCN in this study was comparable to rates reported previously for both microwave ablation and HR.[24–29] Furthermore, we found no differences in patterns of recurrence, liver function on recurrence, or treatment modality for recurrent tumors between groups. Importantly, our results showed that MCN provided almost equivalent oncologic outcomes to HR for single HCC ≤5 cm in size.

We also performed subgroup analyses of OS and RFS related to the preoperative baseline characteristics. Our results showed that HR had better RFS than MCN in patients with tumor size >3 cm (*P* = .029). This better RFS could be associated with the higher local recurrence rate of MCN for larger lesions. In our PSM cohort, the local recurrence rate after MCN was 7%, which is comparable with rates reported previously of 2% to 19% after microwave ablation for HCC.[39–43] It is interesting to note, however, that 6 out of 7 patients who experienced local recurrence after MCN had a tumor size >3 cm. The local recurrence rate of 13% after MCN for tumor size >3 cm was much greater than recurrence rates after our technique of MCN for tumor size ≤3 cm (2%) or after HR for tumor size >3 cm (2%). Tumor size was an important factor associated with local recurrence after local ablative therapy,[39,40] and these findings indicate that HR can be recommended for patients with tumor size >3 cm when patients have good liver function. Further studies are needed

to evaluate more precisely the local tumor control rate of MCN for HCC with tumor size >3 cm.

Another important finding of our study is that patients who underwent MCN had better perioperative outcomes than those who received HR in the PSM cohort. The advantages of MCN were a lesser operation time ($P < .001$), less blood loss ($P < .001$), and lesser postoperative hospital stay ($P < 0.001$) compared with HR. No patients required red blood cell transfusions for intraoperative blood loss in the MCN group, and the major complication rate was <5% in the MCN group. Although a retrospective study reported perforation of other neighboring organs as a major complication of microwave ablation,[44] we did not experience such a severe complication in this study, possibly because our open procedures prevent inadvertent injury to nearby other organs. We place a gauze pad between the ablated area and other organs to ensure a safe operating field, and we cool the ablated area with sufficient cold saline after ablation.[12] Based on these findings, we think that MCN is a safe and less invasive procedure for HCC patients. MCN can be a feasible treatment option, especially for patients with impaired liver function or greater age.

Finally, it should be noted that there is a consensus in both the Western and Asia-Pacific clinical guidelines, that RFA is the mainstay of local ablative therapy, and that RFA is an acceptable alternative to HR for small HCC.[5,6,45] Unfortunately, these guidelines unfortunately concluded that the effectiveness of microwave ablation was under investigation and that its effectiveness remains unclear even though microwave ablation has attracted recent attention worldwide. In addition to the cohort studies comparing microwave ablation and HR, the number of comparative studies of microwave ablation and RFA has also been increasing. The most recent meta-analysis included 4 randomized controlled trials and 10 cohort studies concluded that microwave ablation had similar oncologic outcomes compared with RFA.[46] Our results show comparative outcomes for microwave ablation and HR for primary HCC <5 cm. Therefore, it is our firm belief that microwave ablation deserves to be a recommended ablative treatment for small HCC in these clinical treatment guidelines. We think our results could be helpful in refining current clinical treatment guidelines.

Several limitations of this study should be acknowledged. First, the retrospective design is prone to potential bias. The decision to select HR or MCN depended mainly on preferences of both surgeons and patients, and uncontrolled potentially confounding factors might have influenced outcomes. Although we used a careful, well thought out PSM analysis to minimize selection bias, we may not have avoided selection bias completely in patient matching. Second, this study was based on a single-institution review and might not be representative of other centers. Third, our study spanned an approximately 20-year period, during which HCC treatment has changed substantially. In particular, minimally invasive surgery has developed and has been used commonly to treat HCC during the last 2 decades. Although only a small number of patients underwent a laparoscopic approach in both the HR and MCN groups in our study, greater numbers of patients are expected to undergo a minimally invasive approach in the future. Further analyses are needed to confirm our findings in the next era of minimally invasive surgery.

In conclusion, our PSM results based on long-term follow-up showed that operative MCN provided almost equivalent oncologic outcomes to HR for single HCC ≤5 cm with a less invasive perioperative course. MCN can be a feasible treatment in comparison to HR, especially in patients with impaired liver function or advanced age. HR did, however, have a better RFS than MCN in patients with tumor size >3 cm, and thus HR is recommended for patients with tumor size >3 cm when patients have adequate liver function for HR.

References

1. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: Defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol.* 2006;24:2137—2150.
2. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet.* 2003;362:1907—1917.
3. Kudo M. Management of hepatocellular carcinoma: From surveillance to molecular targeted therapy. *J Gastroenterol Hepatol.* 2010;25:439—452.
4. Edge SB, Byrd DR, Compton CC, et al. *AJCC Cancer Staging Manual.* 7th ed. New York: Springer; 2010.
5. European Association for the Study of the Liver. EASL clinical practice guidelines: Management of hepatocellular carcinoma. *J Hepatol.* 2018;69:182—236.
6. Heimbach JK, Kulik LM, Finn RS, et al. AASLD guidelines for the treatment of hepatocellular carcinoma. *Hepatol.* 2018;68:358—380.
7. Takayama T, Makuuchi M, Hirohashi S, et al. Early hepatocellular carcinoma as an entity with a high cure rate of surgical cure. *Hepatol.* 1998;28:1241—1246.
8. Tateishi R, Shiina S, Teratani T, et al. Percutaneous radiofrequency ablation for hepatocellular carcinoma. An analysis of 1000 cases. *Cancer.* 2005;103:1201—1209.
9. Lau WY, Lai EC. The current role of radiofrequency ablation in the management of hepatocellular carcinoma: A systematic review. *Ann Surg.* 2009;249:20—25.
10. Liang P, Wang Y. Microwave ablation of hepatocellular carcinoma. *Oncol.* 2007;72:124—131.
11. Groeschl RT, Pilgrim CH, Hanna EM, et al. Microwave ablation for hepatic malignancies: A multi-institutional analysis. *Ann Surg.* 2014;259:1195—1200.
12. Takami Y, Ryu T, Wada Y, Saitsu H. Evaluation of intraoperative microwave coagulo-necrotic therapy (MCN) for hepatocellular carcinoma: A single center experience of 719 consecutive cases. *J Hepatobiliary Pancreat Sci.* 2013;20:332—341.
13. Ryu T, Takami Y, Wada Y, Tateishi M, et al. Double- and triple-positive tumor markers predict early recurrence and poor survival in patients with hepatocellular carcinoma within the Milan criteria and Child-Pugh Class A. *J Gastrointest Surg.* 2017;21:957—966.
14. Ryu T, Takami Y, Tsutsumi N, et al. Simultaneous microwave coagulo-necrotic therapy (MCN) and laparoscopic splenectomy for the treatment of hepatocellular carcinoma with cirrhotic hypersplenism. *Surg Today.* 2017;47:548—554.
15. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PL. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatol.* 1994;19:1513—1520.
16. Makuuchi M, Kosuge T, Takayama T, et al. Surgery for small liver cancers. *Semin Surg Oncol.* 1993;9:298—304.
17. Belghiti J, Clavien PA, Gadzijev E, et al. The Brisbane 2000 terminology of liver anatomy and resections. *HBP.* 2000;2:333—339.
18. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: Five-year experience. *Ann Surg.* 2006;250:187—196.
19. Matsushima H, Takami Y, Ryu T, et al. Prognosis of hepatocellular carcinoma patients who achieved long-term recurrence-free survival after curative therapy: Impact of the ALBI grade. *J Gastrointest Surg.* 2018;22:1230—1238.
20. Leyrat C, Caille A, Donner A, Giraudeau B. Propensity score methods for estimating relative risks in cluster randomized trials with low incidence binary outcomes and selection bias. *Stat Med.* 2014;33:3556—3575.
21. Saitsu H, Yoshida M, Taniwaki S, et al. Laparoscopic coagulo-necrotic therapy using Microtase for small hepatocellular carcinoma. *Jpn J Gastroenterol.* 1991;88:2727.
22. Sato M, Watanabe Y, Ueda S, et al. Microwave coagulation therapy for hepatocellular carcinoma. *Gastroenterol.* 1996;110:1507—1514.
23. Seki T, Wakabayashi M, Nakagawa T, et al. Percutaneous microwave coagulation therapy for patients with small hepatocellular carcinoma. *Cancer.* 1999;85:1694—1702.
24. Wang ZL, Liang P, Dong BW, Yu XL, Yu DJ. Prognostic factors and recurrence of small hepatocellular carcinoma after hepatic resection or microwave ablation: A retrospective study. *J Gastrointest Surg.* 2008;12:327—337.
25. Zhang EL, Yang F, Wu ZB, et al. Therapeutic efficacy of percutaneous microwave coagulation versus liver resection for single hepatocellular carcinoma ≤3 cm with Child-Pugh A cirrhosis. *Eur J Surg Oncol.* 2016;42:690—697.
26. Shi J, Sun Q, Wang Y, et al. Comparison of microwave ablation and surgical resection for treatment of hepatocellular carcinomas conforming to Milan criteria. *J Gastroenterol Hepatol.* 2014;29:1500—1507.
27. Li W, Zhou X, Huang Z, et al. Short- and long-term outcomes of laparoscopic hepatectomy, microwave ablation and open hepatectomy for small hepatocellular carcinoma: A 5-year experience in a single center. *Hepatol Res.* 2017;47:650—657.

28. Zhang QB, Zhang XG, Jian R, et al. Microwave ablation versus hepatic resection for the treatment of hepatocellular carcinoma and esophageal variceal bleeding in cirrhotic patients. *Int J Hyperthermia*. 2017;33:255—262.
29. Zhang M, Ma H, Zhang J, He L, Li X. Comparison of microwave ablation and hepatic resection for hepatocellular carcinoma: A meta-analysis. *OncoTargets Ther*. 2017;10:4829—4839.
30. Wada Y, Takami Y, Tateishi M, Ryu T, Mikagi K, Saitsu H. Efficacy of surgical treatment using microwave coagulo-necrotic therapy for unresectable multiple colorectal liver metastases. *OncoTargets Ther*. 2016;9:937—943.
31. Ryu T, Takami Y, Wada Y, Tateishi M, Matsushima H, Yoshitomi M, et al. Oncological outcomes after hepatic resection and/or surgical microwave ablation for liver metastasis from gastric cancer. *Asian J Surg*. 2019;42:100—105.
32. Takami Y, Eguchi S, Tateishi M, Ryu T, Mikagi K, Wada Y, et al. Multimodal treatment of breast cancer liver metastases based on hepatic resection and microwave coagulo-necrotic therapy (MCN). *Int J Cancer Clin Res*. 2016;3.
33. Kotoh K, Morizono S, Kohjima M, Enjoji M, Sakai H, Nakamuta M. Evaluation of liver parenchymal pressure and portal endothelium damage during radio frequency ablation in an in vivo porcine model. *Liver Int*. 2005;25:1217—1223.
34. Kawamoto C, Yamauchi A, Baba Y, Kaneko K, Yakabi K. Measurement of intrahepatic pressure during radiofrequency ablation in porcine liver. *J Gastroenterol*. 2010;45:435—442.
35. Mori Y, Tamai H, Shingaki N, et al. Diffuse intrahepatic recurrence after percutaneous radiofrequency ablation for solitary and small hepatocellular carcinoma. *Hepatol Int*. 2009;3:509—515.
36. Ruzzenente A, Manzoni GD, Molfetta M, et al. Rapid progression of hepatocellular carcinoma after radiofrequency ablation. *World J Gastroenterol*. 2004;10:1137—1140.
37. Llovet JM, Vilana R, Bru C, et al. Increased risk of tumor seeding after percutaneous radiofrequency blation for single hepatocellular carcinoma. *Hepatol*. 2001;33:1124—1229.
38. Kim HJ, Rhim H, Lee MW, Jeong WK. Measurement of intrahepatic pressure during microwave ablation in an ex vivo bovine liver model. *Gut and Liver*. 2015;9:784—790.
39. Liang P, Dong B, Yu X, et al. Prognostic factors for survival in patients with hepatocellular carcinoma after percutaneous microwave ablation. *Radiology*. 2005;235:299—307.
40. Leung U, Kuk D, D'Angelica MI, et al. Long-term outcomes following microwave ablation for liver malignancies. *Br J Surg*. 2015;102:85—91.
41. Martin RC, Scoggins CR, McMasters KM. Safety and efficacy of microwave ablation of hepatic tumors: A prospective review of a 5-year experience. *Ann Surg Oncol*. 2010;17:171—178.
42. Groeschl RT, Wong RK, Quebbeman EJ, et al. Recurrence after microwave ablation of liver malignancies: A single institution experience. *HPB*. 2013;15:365—371.
43. Swan RZ, Sindram D, Martinie JB, Iannitti DA. Operative microwave ablation for hepatocellular carcinoma: Complications, recurrence, and long-term outcomes. *J Gastrointest Surg*. 2013;17:719—729.
44. Liang P, Wang Y, Yu X, Dong B. Malignant liver tumors: Treatment with percutaneous microwave ablation—complications among cohort of 1,136 patients. *Radiol*. 2009;251:933—940.
45. Omata M, Cheng AL, Kokudo N, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: A 2017 update. *Hepatol Int*. 2017;11:317—370.
46. Tan W, Deng Q, Lin S, Wang Y, Xu G. Comparison of microwave ablation and radiofrequency ablation for hepatocellular carcinoma: A systematic review and meta-analysis. *Int J Hyperthermia*. 2019;36:264—272.