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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

Actual 10-Year Survival After Surgical Microwave Ablation for Hepatocellular Carcinoma: A Single-Center Experience in Japan

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ABSTRACT

Background. Little evidence exists regarding long-term survival after microwave ablation for hepatocellular carcinoma (HCC). The aim of this study is to determine actual 10-year survival and clarify the clinicopathological features of patients surviving $\geq$ 10 years after surgical microwave ablation.

Patients and Methods. This retrospective study identified 459 patients who underwent surgical microwave ablation for HCC with curative intent between 2001 and 2008. We compared 100 patients who survived $\geq$ 10 years with 321 patients who died within 10 years.

Results. Median overall survival and recurrence-free survival rates were 5.5 and 2.4 years, respectively. The actual 10-year overall survival rate was 23.8%, and the actual 10-year recurrence-free survival rate was 8.1%. Multivariate analysis showed that age > 70 years [odds ratio 1.87, $P = 0.029$], hepatitis C virus positivity (OR 2.30, $P = 0.004$), Child–Pugh class B (OR 3.28, $P = 0.003$), and platelet count $< 10 \times 10^4$ /μL (OR 1.93, $P = 0.033$) were independent risk factors for actual 10-year survival. During 10-year follow-up, 66% of the $\geq$ 10-year survivors developed recurrence, and 91% of these patients underwent further curative treatment, including hepatic resection or local ablation, for HCC recurrence.

Conclusion. Ten-year survival after surgical microwave ablation for HCC can be expected in approximately 24% of patients, even though nearly 2/3 of our 10-year survival patients experienced recurrence. Close postoperative follow-up and further curative treatment for recurrence are important for improving long-term survival.

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 (HCV) or hepatitis B virus (HBV) infection.[2]

Hepatic resection is generally considered a standard treatment for patients with early-stage HCC,[3] with previous studies reporting 5-year overall survival rates of 40–50%.[4–7] In addition, studies of actual 10-year follow-up and survival data after hepatic resection have been increasing.[8–10] A recent systematic review of 14 retrospective series revealed that 303 actual 10-year survivors had been reported worldwide, with an actual 10-year survival rate of 7%.[11] However, only approximately 20% of all patients presenting with HCC are eligible for resection because of their poor liver function secondary to chronic hepatitis or liver cirrhosis.[12]

Local ablation therapy, such as radiofrequency ablation (RFA) and microwave ablation, is widely used as a therapeutic strategy for small HCC or in patients with impaired liver function for hepatic resection.[13–15] Of these, microwave ablation has attracted recent attention in both Asia and Western countries.[15,16] Several recent studies have found microwave ablation to be an effective treatment for HCC, with reported 5-year overall survival rates of 43–60%.[17–22] However, to the best of the authors' knowledge, little evidence is available regarding actual 10-year survival rates after microwave ablation.

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The aim of this study is to determine the actual number of patients surviving ≥ 10 years after microwave ablation and to identify prognostic factors associated with 10-year survival.

PATIENTS AND METHODS

Patients

We retrospectively analyzed a total of 459 consecutive patients who underwent surgical microwave ablation [microwave coagulo-necrotic therapy (MCN)] for primary HCC from January 2001 to December 2008 in our department. Among these patients, five patients (1%) died within 3 months of operation, 20 patients (4%) died of other or unknown causes, and 13 patients (3%) were lost to follow-up. We excluded these 38 patients from the study and analyzed data for the remaining 421 patients to investigate cancer- or liver-related deaths.

HCC lesions in each patient were preoperatively diagnosed by ultrasonography, dynamic computed tomography, and/or enhanced magnetic resonance imaging. The final diagnosis of HCC was confirmed by pathological examination of tumor biopsy in all patients. Tumors located within 10 mm of the inferior vena cava, hepatic veins, or major Glissonean branches were considered to be in proximity to a major vessel. Tumors located within 10 mm of the liver surface were categorized as being on the surface of the liver.

This study was conducted in accordance with the Declaration of Helsinki and the ethical guidelines for clinical studies of the Ministry of Health, Labor, and Welfare in Japan. The study protocol was approved by the Ethics Committee on Clinical Investigations of Kyushu Medical Center (Approval No. 19C020).

Treatment and Follow-Up

MCN procedures were performed as previously reported.[17,23] We have performed MCN as curative surgical microwave ablation for primary HCC since 1994, and the procedure is well established. MCN was performed by the same surgical team of dedicated liver surgeons led by at least one consultant specialist. We used a 2450-MHz microwave generator system (Alfresa Pharma, Osaka, Japan). 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. We performed MCN as an open approach, including laparotomy, thoracotomy, or laparoscopy, in all patients, with routine intraoperative ultrasound to identify lesions and monitor treatment effect. The ablation area was evaluated by dynamic computed tomography 1–2 weeks after treatment. Perioperative morbidities were stratified by severity based on the Clavien–Dindo classification;[24] major complications were considered grade III or above.

Patients were followed postoperatively every 2–3 months with ultrasound and blood chemistry evaluations. Dynamic computed tomography or enhanced magnetic resonance imaging was performed every 4–6 months. All patients were followed until death or December 2018. Local recurrence was defined as presence of recurrent tumor at the margin of an ablation zone identified on follow-up imaging. When recurrent tumors were found, regardless of the type of recurrence, MCN or hepatic resection was again attempted, based on the same criteria used to select treatment for the initial tumor. However, if MCN or hepatic resection was considered unsuitable to treat multiple recurrences, we performed transcatheter arterial chemoembolization (TACE) or hepatic arterial infusion chemotherapy (HAIC). Patients with extrahepatic metastases were usually treated with sorafenib or radiation therapy.

Statistical Analysis

Continuous variables are presented as median (range) and compared using the Mann–Whitney *U*-test. Categorical variables were compared using Fisher's exact probability method or χ^2 test. Overall survival (OS) was defined as the interval from surgery to death or the date of the last or most recent follow-up visit. Recurrence-free survival (RFS) was defined as the interval from surgery 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 two-tailed tests, with $P < 0.05$ considered statistically significant. All statistical analyses were performed using JMP 12 software (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Among 459 patients who underwent MCN for primary HCC, the median OS was 5.5 years (range 0.4–16.8 years) and the median RFS was 2.4 years (range 0.3–16.8 years). Kaplan–Meier analysis showed that the 1-, 3-, 5-, and 10-year OS rates were 96.9%, 80.1%, 61.9%, and 35.1%, respectively (Fig. 1a), and the 1-, 3-, 5-, and 10-year RFS rates were 84.8%, 45.4%, 30.0%, and 14.8%, respectively (Fig. 1b). After excluding 38 patients who died within

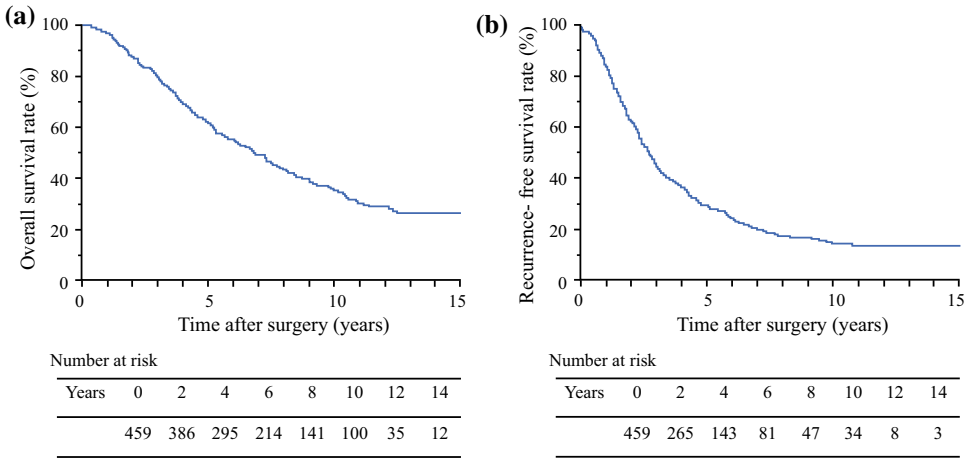

FIG. 1 Long-term survival outcomes after surgical microwave ablation: **a** overall survival and **b** recurrence-free survival rates

3 months of operation, or who died of other or unknown causes or were lost to follow-up, we enrolled 421 patients in this study. Hepatitis C virus (HCV) was the background liver disease in 307 patients (73%), with only 7 patients achieving sustained virological response (SVR) before microwave ablation. Seven patients underwent simultaneous splenectomy for cirrhotic hypersplenism. The number of patients who survived $\geq$ 10 years was 100, with a 10-year actual OS rate of 23.8%. Of these 100 patients, 34 patients survived $\geq$ 10 years without recurrence, with a 10-year actual RFS rate of 8.1%. The clinicopathological characteristics of the 100 patients who survived $\geq$ 10 years versus the 321 patients who survived $<$ 10 years are presented in Table 1. Ten-year survivors were significantly younger, included a lower percentage of HCV-positive status patients, and had better liver function variables and lower tumor numbers. Major complications were experienced by 21 patients (5.0%; eight wound infections, five cases of ascites, four cases of pleural effusion, two intraabdominal abscesses, and two intraabdominal hemorrhages), although there were no surgery-related deaths in this study. Incomplete ablation occurred in nine patients (2.1%) on initial post-MCN imaging. Of the nine patients, five underwent repeat ablation, two underwent TACE, and two received HAIC.

The univariate and multivariate analyses to identify prognostic factors affecting actual 10-year survival and 10-year RFS are presented in Table 2. Multivariate analyses showed that age $>$ 70 years (OR 1.87, $P = 0.029$), HCV-positive status (OR 2.30, $P = 0.004$), Child–Pugh class B (OR 3.28, $P = 0.003$), and platelet count $< 10 \times 10^4/\mu L$ (OR 1.93, $P = 0.033$) were independent risk factors for actual 10-year survival. Multivariate analyses also showed that HCV-positive status (OR 3.21, $P = 0.004$), Child–Pugh class B (OR 3.28, $P = 0.053$), and multiple tumors (OR 1.93, $P = 0.033$) were independent risk factors for actual 10-year RFS.

A comparison of the recurrence characteristics in the two groups is summarized in Table 3. Sixty-seven (67%) of the 100 $\geq$ 10-year survivors and 274/321 (85%) of the $<$ 10-year survivors experienced postoperative HCC recurrence ($P < 0.001$). One of the $\geq$ 10-year survivors experienced recurrence $>$ 10 years after surgery. Local recurrence occurred in 35 patients (8.3%) in this study. Patients with recurrence within 2 years after surgery had significantly shorter survival after recurrence compared with those who developed recurrence after 2 years ($P < 0.001$; Fig. 2a). Patients with single intrahepatic recurrence had significantly longer survival after recurrence compared with those who developed multiple intrahepatic recurrences ($P < 0.001$; Fig. 2b). Extrahepatic recurrences were found in 10 patients (three in bone, two in lung, two in adrenals, two in lymph nodes, and one in brain) of the $<$ 10-year survivors. Repeat MCN was the most common treatment for recurrence and was administered to 50/67 (75%) of the $\geq$ 10-year survivors and 156/274 (57%) of the $<$ 10-year survivors. Only one of the $\geq$ 10-year survivors underwent salvage liver transplantation for recurrence. All 67 of the $\geq$ 10-year survivors were treated for their recurrence, whereas only five of the $<$ 10-year survivors received best supportive care, only. Patients who underwent hepatic resection or local ablation for recurrence had significantly longer survival after recurrence compared with those who underwent other treatment for recurrence ($P < 0.001$; Fig. 2c).

DISCUSSION

Microwave ablation has been used as a local ablation therapy for HCC in Japan since 1988.[25–27] We have performed MCN for HCC for more than 20 years, and previously reported its feasibility and safety in HCC patients.[17,23] The current study presents a large series of patients who underwent surgical microwave ablation for

TABLE 1 Comparison of patients' clinicopathological factors

Characteristic	≥ 10-Year survivors (n = 100)	< 10-Year survivors (n = 321)	P value
Background characteristics			
Age, years, median (range)	67 (44–80)	69 (43–87)	0.004
Sex, male, n (%)	72 (72%)	210 (65%)	0.22
Hepatitis B virus infection, n (%)	25 (25%)	38 (12%)	0.002
Hepatitis C virus infection, n (%)	58 (58%)	249 (78%)	< 0.001
Albumin, g/dL, median (range)	4.1 (3.0–4.9)	3.6 (2.3–4.8)	< 0.001
Total bilirubin, mg/dL, median (range)	0.8 (0.3–2.9)	1.0 (0.3–3.2)	< 0.001
Prothrombin activity, %, median (range)	82 (32–114)	75 (42–164)	< 0.001
ICGR15, %, median (range)	18.1 (3.4–83.7)	24.9 (0.6–81.1)	0.002
Platelets, /μL, median (range)	14.4 (4.4–30.7)	10.1 (3.1–26.3)	< 0.001
Child–Pugh class, A, n (%)	90 (90%)	233 (73%)	< 0.001
Liver cirrhosis, n (%)	24 (24%)	151 (47%)	0.001
Tumor-related factors			
Tumor size, mm, median (range)	23 (11–41)	24 (8–44)	0.226
≤ 3 cm, n (%)	74 (74%)	233 (73%)	0.815
Number of tumors, n (%)			0.034
Single	57 (57%)	136 (42%)	
2–3	24 (24%)	96 (30%)	
> 3	19 (19%)	89 (28%)	
AFP, ng/mL, median (range)	12 (1.1–12,149)	31 (1.5–30,343)	< 0.001
DCP, mAU/mL, median (range)	25 (0–6720)	36 (0–40,400)	0.097
Proximity to major vessel, yes, n (%)	29 (29%)	99 (31%)	0.731
Surface of the liver, yes, n (%)	30 (30%)	102 (32%)	0.716
Surgical factors			
Approach, n (%)			0.154
Laparotomy	46 (46%)	167 (52%)	
Thoracotomy	51 (51%)	151 (47%)	
Laparoscopy	3 (3%)	3 (1%)	
Operating time, min, median (range)	103 (53–210)	101 (40–344)	0.801
Blood loss, g, median (range)	6 (1–106)	10 (1–467)	0.075
Intraoperative blood transfusion, n (%)	3 (3%)	25 (8%)	0.104
Morbidity, n (%)	9 (9%)	26 (8%)	0.829
Complication of Clavien–Dindo grade IIIA or above, n (%)	7 (7%)	14 (4%)	0.190
Postoperative hospital stays, days, median (range)	11 (8–37)	11 (7–59)	0.176

ICGR15 indocyanine green retention rate at 15 min, *AFP* alpha fetoprotein, *DCP* des-gamma carboxy prothrombin

HCC with actual 10-year survival data based on long-term follow-up. Few studies are large enough and include sufficiently long follow-up to provide actual outcomes for HCC patients 10 years after local ablation therapy. To the best of the authors' knowledge, this is the first study to clarify actual long-term survivors and to identify prognostic factors for long-term survival after microwave ablation therapy for patients with HCC.

Some previous studies of long-term follow-up after hepatic resection reported actuarial 10-year OS rates of 12.0–46.3%, with actual 10-year OS rates of 0.9–31.0%.[8–11] In this study, 100 patients survived longer than 10 years, and 34 of these patients had RFS of > 10 years. The 10-year OS rate from our Kaplan–Meier analysis was 35.1%, and the 10-year actual OS rate was 23.8%, both of which are comparable to those reported previously for hepatic resection. On multivariate analysis, higher age, HCV-positive status, Child–Pugh class B, and lower

TABLE 2 Multivariate analysis of factors affecting 10-year survival and 10-year recurrence-free survival in all patients

Characteristic	10-Year survival						10-Year recurrence-free survival					
	Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value	OR	95% CI	*P* value
Age, years (> 70)	1.60	1.01–2.56	0.045	1.87	1.06–3.32	0.029	1.16	0.57–2.42	0.669			
Sex (male)	1.36	0.84–2.25	0.217				1.11	0.52–2.29	0.769			
Hepatitis C virus (positive)	2.50	1.55–4.03	< 0.001	2.30	1.31–4.05	0.004	2.62	1.27–5.35	0.009	3.21	1.46–7.11	0.004
Child–Pugh (class B)	3.40	1.77–7.23	< 0.001	3.28	1.44–8.48	0.003	5.27	1.56–32.9	0.005	3.63	0.98–23.4	0.053
Platelet count ($\times 10^4$ /μL) (< 10)	2.75	1.61–4.84	< 0.001	1.93	1.05–3.64	0.033	2.60	1.14–6.71	0.022	1.63	0.68–4.38	0.283
ICGR15 (%) (> 20)	1.86	1.17–2.95	0.008	1.37	0.79–2.38	0.260	1.11	0.54–2.28	0.767			
AFP (ng/mL) (> 100)	1.29	0.77–2.23	0.329				1.44	0.64–3.69	0.387			
DCP (mAU/mL) (> 100)	1.57	0.92–2.78	0.102				1.83	0.78–5.02	0.171			
Maximum tumor size (mm) (> 30)	1.06	0.64–1.79	0.815				1.02	0.48–2.39	0.952			
Number of tumors (multiple)	1.80	1.24–2.85	0.010	1.49	0.87–2.56	0.147	3.09	1.48–6.95	0.002	2.51	1.12–6.03	0.024
Proximity to major vessel	1.09	0.67–1.82	0.731				2.14	0.92–5.87	0.081			
Surface of the liver	1.09	0.67–1.81	0.712				1.19	0.55–2.46	0.643			
Operating time (min) (> 120)	1.06	0.56–1.96	0.853				2.61	0.93–9.34	0.071			
Blood loss (g) (> 50)	2.43	0.98–7.34	0.054				4.62	0.92–84.2	0.067			
Severe complication	1.86	0.72–4.48	0.190				1.22	0.19–4.58	0.796			

OR odds ratio, *CI* confidence interval, *ICGR15* indocyanine green retention rate at 15 min, *AFP* alpha fetoprotein, *DCP* des-gamma carboxyprothrombin Severe complication: complication of Clavien–Dindo grade IIIA or above

platelet count were independent risk factors for actual 10-year survival. Ten-year survival was not found to be associated with tumor-related factors (size, number, location, or tumor marker levels) or surgical factors. Some previous studies revealed that thrombocytopenia was related to the development of liver cirrhosis and was a risk factor for recurrence and survival in patients with HCC after curative treatment.[28] These findings suggest that HCV infection status and liver function are more important than tumor characteristics when correlating these factors with 10-year survival after surgical microwave ablation.

The HCC recurrence rate after curative treatment is high, with cumulative 5-year recurrence rates > 60%.[29] In our study, 67/100 patients surviving ≥ 10 years experienced recurrence after surgical microwave ablation, and recurrence characteristics and treatment strategy for HCC recurrence are important for longer survival.[8] Intrahepatic recurrence after curative treatment is generally classified into two types: intrahepatic metastasis from the primary tumor and multicentric occurrence of new tumors that differ from the primary lesion[30]. In previous studies, intrahepatic metastasis occurred mainly as early recurrence within 2 years after surgery, while multicentric carcinogenesis resulting from chronic hepatitis or cirrhosis occurred mainly > 2 years after surgery.[30,31] In our study, < 10-year survivors had significantly shorter time to recurrence, with nearly half of these survivors (56%) developing recurrence within 2 years. It is conceivable that these patients experienced intrahepatic metastasis from the primary tumor. In contrast, the majority of ≥ 10-year survivors (87%) developed recurrence > 2 years after surgery. In addition, patients with recurrence within 2 years had significantly shorter postrecurrence survival compared with those developing recurrence > 2 years after surgery ($P < 0.001$). A recent single-center cohort study reported that patients with multicentric occurrence had better prognosis after recurrence than those with intrahepatic metastasis.[32] Considering these findings, although tumor recurrence was common even in ≥ 10-year survivors, the recurrence type in ≥ 10-year survivors was mainly thought to be multicentric occurrence of new tumors.

We also analyzed treatment modalities for recurrence. In previous studies, repeat hepatectomy and local ablation therapy for HCC recurrences, especially for multicentric occurrence, provided better postrecurrence survival

TABLE 3 Recurrence characteristics of patients

Characteristic	≥ 10-Year survivors (n = 100)	< 10-Year survivors (n = 321)	P value
Recurrence, n (%)	67 (67%)	274 (85%)	< 0.001
Local recurrence, n (%)	7 (7%)	28 (9%)	0.162
Recurrence timing, n (%)			< 0.001
< 2 years	9 (14%)	152 (56%)	
2–5 years	32 (48%)	101 (37%)	
5–10 years	25 (38%)	21 (7%)	
> 10 years	1 (1%)	–	
Maximum tumor size, mm, median (range)	19 (9–32)	21 (8–74)	0.026
Number of tumors, n (%)			< 0.001
Single	36 (54%)	90 (33%)	
2–3	22 (34%)	84 (31%)	
> 3	878 (12%)	98 (36%)	
Extrahepatic recurrence, n (%)	0 (0%)	10 (4%)	0.031
Characteristic on recurrence occurrence			
Albumin, g/dL, median (range)	4.0 (2.8–5.0)	3.5 (2.2–5.1)	< 0.001
Total bilirubin, mg/dL, median (range)	0.8 (0.3–2.0)	0.9 (0.2–4.3)	0.023
Prothrombin activity, %, median (range)	88 (60–128)	78 (59–123)	< 0.001
Platelets, /μL, median (range)	13.7 (3.4–29.3)	10.5 (3.4–55.3)	< 0.001
Child–Pugh class, A, n (%)	57 (86%)	183 (67%)	0.009
AFP, ng/mL, median (range)	10 (1.4–3060)	32 (1.5–62,400)	< 0.001
DCP, mAU/mL, median (range)	24 (1–1430)	37 (5–28,400)	0.024
Treatment for recurrence, n (%)			0.003
Resection	7 (10%)	12 (4%)	
vMCN	50 (75%)	156 (57%)	
Percutaneous ablation (RFA or PEIT)	4 (6%)	25 (9%)	
TACE or HAIC	6 (9%)	70 (26%)	
Sorafenib	0 (0%)	4 (1%)	
Radiation	0 (0%)	1 (0%)	
Transplant	1 (1%)	0 (0%)	
BSC	0 (0%)	5 (2%)	

AFP alpha fetoprotein, *DCP* des-gamma carboxyprothrombin, *MCN* microwave coagulo-necrotic therapy, *RFA* radiofrequency ablation, *PEIT* percutaneous ethanol injection therapy, *TACE* transcatheter arterial chemoembolization, *HAIC* hepatic arterial infusion chemotherapy, *BSC* best supportive care

compared with TACE.[32–34] In our study, patients who underwent hepatic resection or local ablation for recurrence had significantly longer postrecurrence survival compared with those who underwent other treatment for recurrence ($P < 0.001$). Although there were many selection biases in the treatment for recurrence in this study, these findings were similar to those in previous studies.[32,33] Furthermore, it must be emphasized that more than half of the ≥ 10-year survivors (54%) had single intrahepatic recurrence and the majority of these survivors (91%) underwent curative treatment, such as hepatic resection or local ablation, for recurrent tumors. Based on these findings, early detection of recurrence and further curative treatment for HCC recurrence are important for improving long-term survival in patients with HCC after microwave ablation.

Finally, it should be noted that control of HCV infection and preserving liver function are critically important for long-term survival in patients with HCC. This is because these factors were independent prognostic factors for actual 10-year OS and RFS in our study. Approximately 70% of all HCC patients have HCV infection in Japan,[35] and active HCV infection is one of the most important factors in intrahepatic recurrence after curative treatment, particularly multicentric recurrence.[36] In recent studies, achieving SVR before HCC occurrence reduced recurrence and improved long-term outcomes after curative treatment in

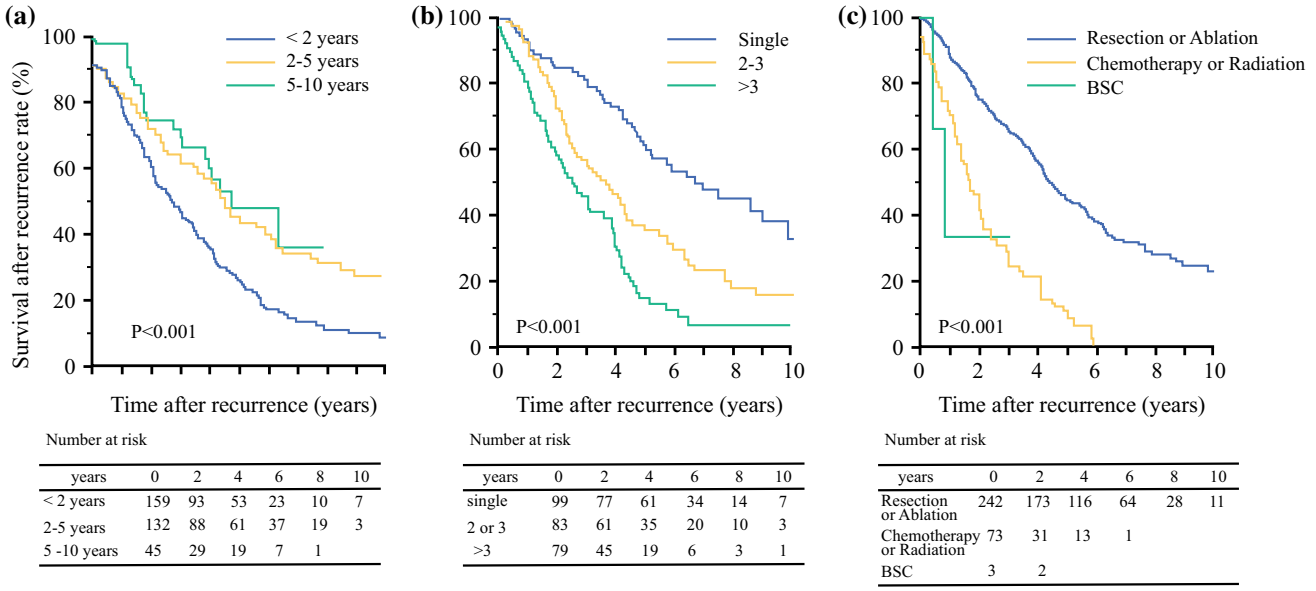

FIG. 2 Overall survival rates after recurrence according to **a** time to recurrence, **b** number of intrahepatic recurrences, and **c** treatment for recurrent tumors

HCV-related HCC patients.[37,38] Additionally, the number of patients with HCV achieving SVR has dramatically increased secondary to direct-acting antiviral agents (DAAs) in recent years.[39,40] Unfortunately, only 7/307 HCV-positive patients (2.3%) in our study achieved SVR before HCC occurrence. This is because all patients enrolled in this study underwent microwave ablation before 2008, before the introduction of DAAs. Most patients with HCV infection are expected to achieve SVR through administration of DAAs in the future, which is hoped will improve long-term outcomes in HCV-related HCC patients. Future analyses are required to examine the long-term outcomes in HCV-related HCC patients following the introduction of DAAs.

Several limitations of this study should be acknowledged. First, the retrospective design is prone to potential bias. Second, this study was based on a review from a single-institution and might not represent findings in other centers. Nevertheless, we believe that our results may be clinically informative and could be an indicator for future investigation of microwave ablation for HCC patients.

CONCLUSIONS

The results of this study suggest that 10-year survival after surgical microwave ablation for HCC is possible and can be expected in approximately 24% of patients, but tumor recurrence is common even in ≥ 10-year survivors. The ≥ 10-year survivors who experienced recurrence had later recurrence, had fewer recurrent tumors with preserved liver function, and underwent curative treatment for recurrent tumors more frequently. Close postoperative follow-up and further curative treatment for recurrence are important for improving long-term survival of HCC patients after microwave ablation.

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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;24:2137–50.
2. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. *Lancet.* 2003;362:1907–17.
3. Takayama T, Makuuchi M, Hirohashi S, et al. Early hepatocellular carcinoma as an entity with a high cure rate of surgical cure. *Hepatology.* 1998;28:1241–46.
4. Chapman WC, Klintmalm G, Hemming A, et al. Surgical treatment of hepatocellular carcinoma in North America: can hepatic resection still be justified? *J Am Coll Surg.* 2015;220:628–37.
5. Shah SA, Cleary SP, Wei AC, et al. Recurrence after liver resection for hepatocellular carcinoma: risk factors, treatment, and outcomes. *Surgery.* 2007;141:330–9.
6. Arii S, Yamaoka Y, Futagawa S, et al. Results of surgical and non-surgical treatment for small-sized hepatocellular carcinomas:

a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. *Hepatology.* 2000;32:1224–9.
7. Grazi GL, Ercolani G, Pierangeli F, et al. Improved results of liver resection for hepatocellular carcinoma on cirrhosis give the procedure added value. *Ann Surg.* 2001;234:71–7.
8. Franssen B, Jibara G, Tabrizian P, et al. Actual 10-year survival following hepatectomy for hepatocellular carcinoma. *HPB.* 2014;16:830–5.
9. Shimada K, Sano T, Sakamoto Y, et al. A long-term follow up and management study of hepatocellular carcinoma patients surviving for 10 years or longer after curative hepatectomy. *Cancer.* 2005;104:1939–47.
10. Zheng J, Kuk D, Gonen M, et al. Actual 10-year survivors after resection of hepatocellular carcinoma. *Ann Surg Oncol.* 2017;24:1358–66.
11. Gluer AM, Cocco N, Laurence JM, et al. Systematic review of actual 10-year survival following resection for hepatocellular carcinoma. *HPB.* 2012;14:285–90.
12. Bruix J, Sherman M. American Association for the Study of Liver Disease. Management of hepatocellular carcinoma: an update. *Hepatology* 2011;53:1020–2.
13. Tateishi R, Shiina S, Teratani T, et al. Percutaneous radiofrequency ablation for hepatocellular carcinoma. An analysis of 1000 cases. *Cancer.* 2005;103:1201–9.
14. Lau WY, Lai EC. The current role of radiofrequency ablation in the management of hepatocellular carcinoma: a systematic review. *Ann Surg.* 2009;249:20–5.
15. Liang P, Wang Y. Microwave ablation of hepatocellular carcinoma. *Oncology.* 2007;72:124–31.
16. Groeschl RT, Pilgrim CH, Hanna EM, et al. Microwave ablation for hepatic malignancies: a multiinstitutional analysis. *Ann Surg.* 2014;259:1195–200.
17. Takami Y, Ryu T, Wada Y, et al. Evaluation of intraoperative microwave coagulo-necrotic therapy (MCN) for hepatocellular carcinoma: a single center experience of 719 consecutive cases. *J Hepatobiliary Pancreat Sci.* 2013;20:332–41.
18. 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.
19. Lloyd DM, Lau KN, Welsh F, et al. International multicentre prospective study on microwave ablation of liver tumours: preliminary results. *HPB.* 2011; 13: 579–85.
20. 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;17:171–8.
21. Groeschl RT,Wong RK, Quebbeman EJ, et al. Recurrence after microwave ablation of liver malignancies: a single institution experience. *HPB.* 2013;15:365–71.
22. Swan RZ, Sindram D, Martinie JB, et al. Operative microwave ablation for hepatocellular carcinoma: complications, recurrence, and long-term outcomes. *J Gastrointest Surg.* 2013;17:719–29.
23. 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;47:548–54.
24. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien–Dindo classification of surgical complications: five-year experience. *Ann Surg.* 2006;250:187–96.
25. Saitsu H, Yoshida M, Taniwaki S, et al. Laparoscopic coagulonecrotic therapy using Microtase for small hepatocellular carcinoma. *Jpn J Gastroenterol.* 1991;88:2727.
26. Sato M, Watanabe Y, Ueda S, et al. Microwave coagulation therapy for hepatocellular carcinoma. *Gastroenterology.* 1996;110:1507–14.
27. Seki T, Wakabayashi M, Nakagawa T, et al. Percutaneous microwave coagulation therapy for patients with small hepatocellular carcinoma. *Cancer.* 1999;85:1694–702.
28. Lu SN, Wang JH, Liu SL, et al. Thrombocytopenia as surrogate for cirrhosis and a marker for the identification of patients at high risk for hepatocellular carcinoma. *Cancer.* 2006;107:2212–22.
29. Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. *Semin Liver Dis.* 2005;25:181–200.
30. Takenaka K, Kawahara N, Yamamoto K, et al. Results of 280 liver resections for hepatocellular carcinoma. *Arch Surg.* 1996;131:71–6.
31. Yamamoto J, Kosuge T, Takayama T, et al. Recurrence of hepatocellular carcinoma after surgery. *Br J Surg.* 1996;83:1219–22.
32. Huang ZY, Liang BY, Xiong M, et al. Long-term outcomes of repeat hepatic resection in patients with recurrent hepatocellular carcinoma and analysis of recurrent types and their prognosis: a single-center experience in China. *Ann Surg Oncol.* 2012;19:2515–25.
33. Ho CM, Lee PH, Shau WY, et al. Survival in patients with recurrent hepatocellular carcinoma after primary hepatectomy: comparative effectiveness of treatment modalities. *Surgery.* 2012; 151:700–9.
34. 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;22:1230–8.
35. Umemura T, Ichijo T, Yoshizawa K,et al. Epidemiology of hepatocellular carcinoma in Japan. *J Gastroenterol.* 2009;44:102–7.
36. Ikeda K, Arase Y, Kobayashi M, et al. Significance of multicentric cancer recurrence after potentially curative ablation of hepatocellular carcinoma: a longterm cohort study of 892 patients with viral cirrhosis. *J Gastroenterol.* 2003;38:865–76.
37. Shinkawa H, Hasegawa K, Arita J, et al. Impact of sustained virological response to interferon therapy on recurrence of hepatitis C virus-related hepatocellular carcinoma. *Ann Surg Oncol.* 2017;24:3196–202.
38. Ryu T, Takami Y, Wada Y, et al. Effect of achieving sustained virological response before hepatitis C virus-related hepatocellular carcinoma occurrence on survival and recurrence after curative surgical microwave ablation. *Hepatol Int.* 2018;12:149–57.
39. Kanogawa N, Ogasawara S, Chiba T, et al. Sustained virologic response achieved after curative treatment of hepatitis C virus-related hepatocellular carcinoma as an independent prognostic factor. *J Gastroenterol Hepatol*. 2015;30:1197–204.
40. Conti F, Buonfiglioli F, Scuteri A, et al. Early occurrence and recurrence of hepatocellular carcinoma in HCV-related cirrhosis treated with direct-acting antivirals. *J Hepatol.* 2016;65:727–33.