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Multimodal radiofrequency ablation versus laparoscopic hepatic resection for the treatment of primary hepatocellular carcinoma within Milan criteria in severely cirrhotic patients: long-term favorable outcomes over 10 years

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Abstract

Background Less invasiveness is an important consideration for the treatment of hepatocellular carcinoma (HCC) especially in patients with severe cirrhosis.

Methods Between April 2000 and September 2016, 100 patients with liver damage B underwent multimodal radiofrequency ablation (RFA; $n=62$) or laparoscopic hepatic resection (Lap-HR; $n=38$) for primary HCC as defined by the Milan criteria. We compared the operative outcomes and patients' survival between the two groups.

Results The RFA group showed worse liver functions as indicated by indocyanine green retention rate (32.9 vs. 22.4%; $p<0.0001$) and serum albumin value (3.3 vs. 3.6 g/dl; $p=0.0029$). As expected, RFA was less invasive, as indicated by the differences in operation time (166 vs. 288 min.; $p<0.0001$) and blood loss (8 vs. 377 g; $p<0.0001$). There was no significant difference in the morbidity rate between the two groups; however, the duration of hospital stay of the RFA group was significantly shorter (7 vs. 11 days; $p=0.0002$). There were no significant between-group differences regarding overall or disease-free survival.

Conclusion Multimodal RFA for HCC in patients with severe cirrhosis is associated with less invasiveness and shorter hospital stays, with no compromise in the patients' survival. In patients with severe cirrhosis, it may be time to consider changing the standard treatment for primary HCC within the Milan criteria to multimodal RFA.

Keywords Radiofrequency ablation (RFA) · Laparoscopic hepatic resection (Lap-HR) · Hepatocellular carcinoma (HCC) · Liver damage · Overall survival (OS) · Disease-free survival (DFS)

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide. Its incidence has doubled in the past 20 years, making it the second leading cause of cancer death worldwide [1]. The mainstay of curative treatment for HCC is hepatic resection (HR), and the surgical results of HR for HCC have significantly improved, with the mortality rate nearly reaching zero [2]. However, HR for HCC remains a high-risk procedure, especially in patients with cirrhosis. As a less invasive surgery for HCC, laparoscopic hepatic resection (Lap-HR) has been developed, and we have advocated its use as a standard procedure for treatment of primary HCC cases falling within the Milan criteria [3] (i.e., ≤ 5 cm in dia. in single HCC or ≤ 3 nodules and ≤ 3 cm in dia. in multiple HCCs) [4].

Radiofrequency ablation (RFA) is another alternative in the management of HCC. It is to be expected that local control of HCC by RFA would be inferior to that of HR; however, various efforts to accomplish complete necrosis by multimodal RFA such as laparoscopic [5] or thoracoscopic

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[6] approaches, and salvage RFA [7] achieved clinical outcomes comparable with those of HR. According to the Barcelona Clinic Liver Cancer (BCLC) staging system [8] and Japanese evidence-based guidelines [9], either HR or RFA is recommended for HCC ≤ 3 cm. Recent meta-analysis revealed that the clinical effectiveness of RFA is comparable to HR, with fewer complications but higher recurrence, especially for patients with HCC ≤ 2 cm [10]. However, which treatment to apply to what kind of patients remains an issue on which opinion is divided.

Previous studies suggest that the survival impacts of aggressive HR for HCC were less in patients with severe liver cirrhosis such as liver damage B [11, 12]. As for intrahepatic recurrence, not only intrahepatic metastasis, but also multi-centric recurrence play an important role after treatment. As reported previously [11], patients with liver damage B already have higher risk of multi-centric recurrence; therefore, the impact of eradicating micro-metastasis by resection at the initial treatment would decrease. We have developed a hypothesis that, in such patients, less invasive treatment by RFA may be preferable to Lap-HR.

We herein present a retrospective analysis of the long-term results of RFA and Lap-HR for primary HCC within the Milan criteria in patients with severe cirrhosis classified as liver damage B over a 10-year period.

Methods

Patient characteristics

We retrospectively analyzed 100 patients with liver damage B who underwent multimodal RFA or Lap-HR for primary HCC within the Milan criteria at the Department of Gastroenterological Surgery, Kumamoto University, or Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, from April 2000 to September 2016. We divided this cohort into two groups: the RFA group ($n = 62$), and the Lap-HR group ($n = 38$). This study was approved by the Human Ethics Review Committee of both institutions.

Surgical procedures of Lap-HR and RFA

Details of our techniques of RFA have been also reported previously [13]. Percutaneous RFA, RFA accompanied laparotomy, laparoscopic RFA, RFA accompanied thoracotomy, thoracoscopic RFA, or a multimodal combination was selected according to the HCC locations [5, 6]. Details of our surgical techniques of Lap-HR and patient selection criteria for Lap-HR for HCC have been reported [4]. Essentially, HR was selected for the treatment if possible. The reasons for undergoing RFA rather than HR included ill-located HCC requiring major HR, insufficient remnant liver functional reserve, high operative risks associated with general condition, and refusal of HR by patients [14].

Any death that occurred in the hospital after treatments was recorded as a mortality. Complications were evaluated by Clavien's classification, and complications with a score of Grade II or more were defined as positive [15].

Follow-up and treatment strategy for recurrent HCC

Dynamic computed tomography (CT) was performed approximately 7 days after RFA or Lap-HR to confirm the eradication of HCC by HR or the necrosis area by RFA in all patients. Complete ablation was defined as the absence of contrast enhancement within the entire tumor. RFA was repeated if an unablated tumor remnant was suspected to remain.

After discharge, all patients were examined for recurrence by dynamic CT and tumor markers such as α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP) every 3 months [4]. The mean follow-up period was 3.1 years (range 0.1–13.4 years) in the Lap-HR group, and 4.8 years (range 0.2–13.7 years) in the RFA group.

When recurrence was suspected, we treated the recurrent HCC by repeat HR [16], by ablation therapy, or by lipiodolization [17].

Statistics

Continuous variables are expressed as the means ± standard deviations (SDs) and were compared using Student's t-test. Categorical variables were compared using the χ^2 test. The survival curves were generated by the Kaplan–Meier method and compared using the log-rank test. All analyses were performed with JMP Pro 12.2.0 (SAS Institute Inc., Cary, NC). P values less than 0.05 were considered significant.

Results

Procedures of Lap-HR or RFA

Of the 62 multimodal RFA patients, percutaneous RFA was performed in 34 (55%), laparoscopic RFA in 14 (23%), laparoscopic + percutaneous RFA in 5 (8%), thoracoscopic RFA in 7 (11%), while RFA accompanied laparotomy in 2 (3%).

All laparoscopic 40 HRs in 38 patients were minors. Laparoscopic partial HR was applied to 28 patients (74%), and 4 patients (11%) underwent two partial HRs. Laparoscopic left lateral sectionectomy to 8 patients (21%), and laparoscopic anatomical segmentectomy (Segment 3 or Segment 5) to 2 patients (5%) were performed. Overall, 22 patients (58%) underwent pure Lap-HR, and RFA was simultaneously applied to other HCCs in 2 patients (3%). We determined the indication of HR for HCC according to the 3rd Japan Society of Hepatology (JSH)-HCC guidelines [18] rather than the Barcelona Clinic Liver Cancer system [19]; therefore, six patients (16%) with multifocal HCC underwent HR.

Comparisons of patients' backgrounds, surgical factors, and tumor-related factors

Patient backgrounds, surgical factors, and tumor-related factors are summarized in Table 1. As for patient backgrounds, the mean value of serum albumin was significantly lower in the RFA group (3.3 ± 0.4 vs. 3.6 ± 0.4 g/dl; $p = 0.0029$). The mean value of indocyanine green retention rate at 15 min. (ICGR15) was significantly higher in the RFA group (32.9 ± 10.0 vs. 22.4 ± 7.8%; $p < 0.0001$).

As for surgical factors, less invasiveness was accomplished in the RFA group as indicated by the shorter operation time (166 ± 130 vs. 284 ± 105 min.; $p < 0.0001$) and lower blood loss (8 ± 15 vs. 377 ± 635 g; $p < 0.0001$). Zero mortality was achieved in both groups. Irrespective of the RFA procedure being less invasive, there was no significant difference in the morbidity rate between the two groups (10 vs. 8%; $p = 0.5854$).

As for tumor-related factors, the mean value of tumor size was significantly smaller in the RFA group (2.0 ± 0.6 vs. 2.4 ± 0.9 cm; $p = 0.0222$). The rate of multiplicity of HCC was higher in the RFA group (32%) compared to that in the Lap-HR group (16%); however, this difference was not statistically significant ($p = 0.0617$).

Comparisons of patient backgrounds, surgical factors, and tumor-related factors between the percutaneous RFA group ($n = 34$) and the surgical RFA group ($n = 28$) are summarized in Table 2. There were no significant differences both in patient backgrounds and tumor-related factors. As for operation time and blood loss, there were no significant differences; however, the hospital stay of the surgical RFA group was significantly longer than that of the percutaneous RFA group (8 ± 3 vs. 7 ± 3 days; $p = 0.0394$).

Table 1 Comparisons of patient backgrounds, surgical factors, and tumor-related factors between the RFA group ($n = 62$) and the Lap-HR group ($n = 38$)

Variables	RFA ($n = 62$)	Lap-HR ($n = 38$)	p values
Patient backgrounds			
Age	66.5 ± 9.5	66.9 ± 9.1	0.8581
Male/female	40/22	25/13	0.8968
HBs-Ag (+) (%)	9 (15%)	5 (13%)	0.3733
HCV-Ab (+) (%)	45 (73%)	30 (79%)	0.4719
T-bil (mg/dl)	1.0 ± 0.5	1.0 ± 0.6	0.9443
Alb (g/dl)	3.3 ± 0.4	3.6 ± 0.4	0.0029
ICGR-15	32.9 ± 10.0	22.4 ± 7.8	< 0.0001
Child–Pugh B (%)	8 (13%)	5 (13%)	0.9707
AFP (ng/ml)	94 ± 202	291 ± 1320	0.2478
DCP (mAU/ml)	99 ± 244	141 ± 329	0.4770
Surgical factors			
Operation time (min)	166 ± 130	284 ± 105	< 0.0001
Blood loss (g)	8 ± 15	377 ± 635	< 0.0001
Transfusion (+) (%)	0 (0%)	1 (3%)	0.2353
Mortality (+) (%)	0 (0%)	0 (0%)	0.9999
Morbidity (+) (%)	6 (10%)	3 (8%)	0.5854
Hospital stay (days)	7 ± 3	11 ± 5	0.0002
Tumor-related factors			
Tumor size (cm)	2.0 ± 0.6	2.4 ± 0.9	0.0222
Solitary/multiple	42/20	32/6	0.0617
Stage II/III (%)	40 (65%)	27 (71%)	0.4978

HBS-Ag hepatitis B virus surface antigen, *HCV-Ab* hepatitis C antibody, *T-bil* total bilirubin, *Alb* albumin, *ICGR-15* indocyanine green retention rate at 15 min, *AFP* alpha fetoprotein, *DCP* des-gama-carboxy prothrombin

Table 2 Comparisons of patient backgrounds, surgical factors, and tumor-related factors between the percutaneous RFA group ($n = 34$) and the surgical RFA group ($n = 28$)

Variables	Percutaneous RFA ($n = 34$)	Surgical RFA ($n = 28$)	p values
Patient backgrounds			
Age	65.9 ± 8.9	67.3 ± 10.4	0.5849
Male/female	24/10	16/12	0.2984
HBs-Ag (+) (%)	4 (12%)	5 (18%)	0.4980
HCV-Ab (+) (%)	27 (79%)	18 (64%)	0.2544
T-bil (mg/dl)	1.0 ± 0.5	1.1 ± 0.4	0.3730
Alb (g/dl)	3.3 ± 0.3	3.3 ± 0.4	0.4907
ICGR-15	32.1 ± 8.7	34.0 ± 11.6	0.4938
Child–Pugh B (%)	5 (15%)	3 (11%)	0.7192
AFP (ng/ml)	113 ± 233	71 ± 158	0.4163
DCP (mAU/ml)	74 ± 177	131 ± 307	0.3634
Surgical factors			
Operation time (min)	175 ± 159	155 ± 80	0.5682
Blood loss (g)	10 ± 19	6 ± 6	0.3581
Transfusion (+) (%)	0 (0%)	0 (0%)	0.9999
Mortality (+) (%)	0 (0%)	0 (0%)	0.9999
Morbidity (+) (%)	3 (9%)	3 (11%)	0.8021
Hospital stay (days)	7 ± 3	8 ± 3	0.0394
Tumor-related factors			
Tumor size (cm)	2.0 ± 0.6	2.0 ± 0.6	0.9298
Solitary/multiple	20/14	22/6	0.1116
Stage II/III (%)	25 (74%)	15 (54%)	0.1181

HBS-Ag hepatitis B virus surface antigen, *HCV-Ab* hepatitis C antibody, *T-bil* total bilirubin, *Alb* albumin, *ICGR-15* indocyanine green retention rate at 15 min, *AFP* alpha fetoprotein, *DCP* des-gama-carboxy prothrombin

Patient survival

The overall survival (OS) curves are shown in Fig. 1A, and disease-free survival (DFS) curves are shown in Fig. 1B. There were no significant differences in either OS ($p = 0.9245$) or DFS ($p = 0.8870$) between the two groups. The 5-year OS rate was 85% in the RFA group, and 76% in the Lap-HR group, respectively. The 2-year DFS rate was 55% in the RFA group, and 57% in the Lap-HR group, respectively. There were no port site or needle tract recurrences or peritoneal seedings of HCC in either groups.

No patients in the Lap-HR group had local recurrence. On the other hand, three patients (5%) had local recurrence in the RFA group. The rate of local recurrence of the RFA group was higher, but the difference was not statistically significant ($p = 0.0872$). All three patients underwent salvage HR successfully.

Discussion

We previously reported that liver dysfunction is one of the major risk factors for postoperative complications after HR in patients with HCC [20]. In addition, postoperative complications are reported to be associated with poor prognosis in patients with HCC [21]. Therefore, less invasiveness is a serious concern when treating HCC in severely cirrhotic patients. A recent meta-analysis revealed that Lap-HR was associated with lower incidences of postoperative ascites and liver failure compared to Open-HR without any disadvantage in oncological outcomes [22]. We reported very similar same results concerning of the superiority of Lap-HR [4]. To further reduce invasiveness, RFA is a potent option. Our current study could not demonstrate a decrease of the rate of postoperative complications in RFA compared with Lap-HR; however, a recent meta-analysis revealed that RFA could lead to a decrease of the postoperative complication rate [10].

As for oncological outcomes, if the patient's remnant liver functional reserve permits, HR is recommended for HCC rather than RFA because of the high rate of local recurrence of RFA [7, 10]. Most RFA procedures are performed percutaneously, and it is difficult to apply RFA to HCC located at the liver surface. This problem is one of the major causes of local recurrence of RFA-treated cases [21]. We have applied "multimodal" RFA combining various approaches such as laparoscopy and thoracoscopy [5, 6]. In our series, good oncological outcomes such as 85% of 5-year OS and 55% of 5-year DFS by RFA were gained. One of the major reasons for this good patient prognosis after RFA would be our multimodal approach, which enabled easy access to HCC and led to good ablation effects. Another important strategy for RFA is salvage treatment for local recurrence of RFA. As we emphasized previously [7], a recent meta-analysis reported that RFA has comparable oncological results with HR if local recurrence of HCC after RFA can be detected in a timely manner and effectively treated [23]. From the view point of multistep carcinogenesis of HCC, severe liver cirrhosis is already pre-cancerous, and has a higher risks for multi-centric HCC recurrence [24]. In such patients, RFA as an initial treatment for HCC along with a careful "wait and see policy" for local recurrence would allow timely salvage HR to be applied. In addition, we recommended not repeat HR but salvage transplantation for recurrent HCC in patients with liver damage B [12]. To avoid intraabdominal adhesion by initial treatment, RFA is preferable to Lap-HR.

Generally, the Child–Pugh classification is used for liver functional assessments in patients with HCC [7]. The Japanese guideline adopted the liver damage criteria proposed by the Liver Cancer Study Group of Japan which included the ICGR15 value [25]. The value of ICGR15 was reported to be the only marker that reliably predicts liver failure and

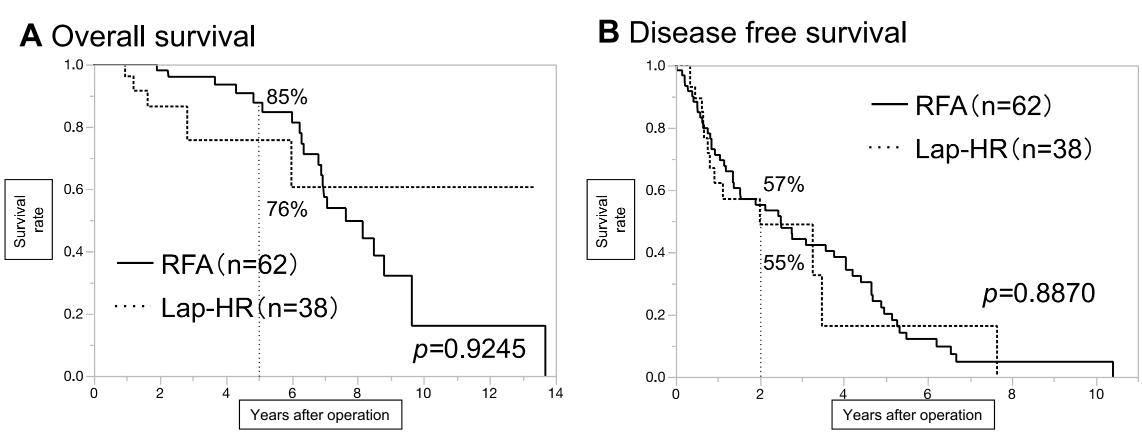

Fig. 1 Overall survival (**A**) and disease-free survival (**B**) curves after treatments in severely cirrhotic patients with HCC within the Milan criteria who underwent RFA ($n = 62$) or Lap-HR ($n = 38$)

mortality after HR [26]. We have reported that the degree of liver damage was more useful than the Child–Pugh classification at predicting the incidence of morbidity and the prognosis of patients with HCC [11, 12]. Therefore, our study used the severity of cirrhosis as a stand-in for degree of liver damage in assessing liver dysfunction.

Another concern of RFA is that incomplete necrosis could lead to cancer stemness or epithelial mesenchymal transition of HCC cells, and lead to intrahepatic dissemination or distant metastasis [27, 28]. However, in this series, there were no patients with such unusual recurrences after RFA. RFA for HCC with microvascular invasion (MVI) could lead such metastases. DCP is not a standardized variable yet by many liver surgeons in the world; however, especially in Japan, the preoperative DCP value was reported to be important in predicting MVI in HCC [29]. The major predictor for MVI in small HCC is high DCP $\geq$ 100 mAU/ml, as we reported [30]. In the subgroup analysis of patients with DCP $\geq$ 100 mAU/ml ($n = 18$), the oncological disadvantage of RFA does not appear (data not shown).

The major limitation of our study was that this study consisted of a relatively small number of selected patients. All HCC patients with liver damage B to whom HR could be safely applied did not necessary undergo HR for various reasons such as poor general status or refusal. The indication for Open-HR or Lap-HR was not completely consistent. In addition, for example, comparing only laparoscopic left lateral sectionectomies and RFA of segments II/III may be a better comparison than all patients. Therefore, a prospective study may be needed to confirm our result.

In conclusion, multimodal RFA for HCC in patients with severe cirrhosis is associated with less invasiveness and shorter hospital stays, with no compromise in the patients' survival. In patients with severe cirrhosis, it may be time to consider changing the standard treatment for primary HCC within the Milan criteria to multimodal RFA.

Compliance with ethical standards

Disclosures Yo-ichi Yamashita, Katsunori Imai, Takayoshi Kaida, Takanobu Yamao, Masayo Tsukamoto, Shigeki Nakagawa, Hirohisa Okabe, Akira Chikamoto, Takatoshi Ishiko, Tomoharu Yoshizumi, Tetsuo Ikeda, Yoshihiko Maehara, and Hideo Baba have no conflict of interest or financial ties to disclose.

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