Scientific Research Publishing

Open Journal of Radiology, 2017, 7, 177-189
http://www.scirp.org/journal/ojrad
ISSN Online: 2164-3032
ISSN Print: 2164-3024

Effectiveness of Radiofrequency Ablation of Initial Recurrent Hepatocellular Carcinoma after Hepatectomy: Long-Term Results and Prognostic Factors

Ken Shinozuka[1], Toshiya Shibata[1,2*], Rinpei Imamine[1], Masako Kataoka[1], Kaori Togashi[1]

[1]Department of Radiology, Kyoto University Graduate School of Medicine, Kyoto, Japan
[2]Department of Radiology, Kyoto College of Medical Science, Kyoto, Japan
Email: *shibata@kyoto-msc.jp

How to cite this paper: Shinozuka, K., Shibata, T., Imamine, R., Kataoka, M. and Togashi, K. (2017) Effectiveness of Radiofrequency Ablation of Initial Recurrent Hepatocellular Carcinoma after Hepatectomy: Long-Term Results and Prognostic Factors. *Open Journal of Radiology*, **7**, 177-189.
https://doi.org/10.4236/ojrad.2017.73020

Received: July 25, 2017
Accepted: August 28, 2017
Published: August 31, 2017

Abstract

Background: Intrahepatic recurrence of hepatocellular carcinoma (HCC) is frequently noted in patients after hepatectomy of HCC. Recurrence HCC is usually diagnosed as small nodule ≤ 2 cm in diameter due to the frequent postoperative check up with US, dynamic CT, or dynamic EOB-MRI. Radiofrequency ablation (RFA) is recommended for these small HCCs, because RFA is minimally invasive, effective, and repeatedly performed. Purpose: To investigate the long-term outcome and prognostic factors of RFA in recurrent HCC after heaptectomy. Material and Methods: Between February 2002 and October 2011, 75 patients with initial intrahepatic recurrence of HCC after hepatectomy underwent RFA. The 57 patients were men and 18 women, whose age ranged from 44 years to 83 years (median, 69 years). Sixty-nine patients had a single nodule and 6 patients had two nodules. The size of the 81 nodules ranged 5 - 30 mm (median, 15 mm). Regular follow-up after RFA was performed to evaluate rates of local tumor progression, overall survival rates, and disease-free survival rates. Prognostic factors related to overall survivals and disease-free survivals were evaluated, too. Results: During follow-up periods after RFA (3 to 151 months, median, 55 months), local recurrence was noted in 10 nodules of 10 patients (10/81 nodules = 12.3%). The rates of local recurrence of 1-yr, 3-yr, 5-yr, and 8-yr were 7.6%, 12.0%, 12.0%, and 12.0%, respectively. During the follow-up periods, 36 patients were alive and 39 died. The cumulative overall survival rates of 1-yr, 3-yr, 5-yr, and 10-yr were 97.3%, 79.1%, 56.6%, and 32.2%, respectively. The cumulative disease-free survival rates of 1-yr, 3-yr, and 5-yr were 42.7%, 18.8%, and 12.6%, respectively.

Child-Pugh Class (A or B) before RFA for a recurrent HCC was a significant prognostic predictor of overall survival rates ($p = 0.007$), and Child-Pugh class (A or B) before hepatectomy was that of disease-free survival rates ($p = 0.004$). Conclusion: RFA was an effective, useful therapeutic option for treatment of recurrent HCC after hepatectomy. Child-Pugh Class (A or B) before RFA was a significant prognostic predictor of long-term survival, and Child-Pugh class (A or B) before hepatectomy was a significant prognostic predictor of disease-free survival.

Keywords

Hepatocellular Carcinoma (HCC), Recurrent HCC, Radiofrequency Ablation (RFA)

1. Introduction

Hepatectomy is an established curative treatment for hepatocellular carcinoma (HCC), and now performed worldwide [1]. However, intrahepatic recurrence of HCC is frequently noted in patients after hepatectomy of HCC. The incidence of intrahepatic recurrence has been reported to be as high as 70% at 5 years after hepatectomy [2] [3]. The treatment options for intrahepatic recurrent HCC are various, including repeated hepatectomy, radiofrequency ablation (RFA), or transcatheter chemoembolization (TACE) [4] [5] [6]. Indeed, the treatment algorithm for recurrent HCC varies from center to center. Although repeated hepatectomy would be a curative treatment [3], most patients might not be candidates for hepatectomy because of the small remnant liver or inadequate hepatic function. RFA is an effective treatment for small HCC ≤ 3 cm, whose results are comparable to those of hepatectomy. There are a number of studies describing the effectiveness of RFA for recurrent HCC after hepatectomy [4] [5] [7] [8] [9].

In our hospital, surgeons and radiologists had consequence that RFA was a first-line treatment for the initial intrahepatic recurrence of small HCC ≤ 3 cm after hepatectomy, because of the good local control and low invasiveness. The purpose of this study was to retrospectively evaluate the effectiveness of RFA for the treatment of intrahepatic recurrent HCC after hepatectomy.

2. Materials and Methods

The institutional review board approved this retrospective study, and written informed waved (E-2127).

Between February 2002 and October 2011, 75 patients who underwent hepatectomy for HCC at our department of surgery and developed initial intrahepatic recurrence during postoperative follow-up periods, were referred to department of radiology for RFA. Our criteria for percutaneous RFA included: 1) no-

dular size ≤ 3 cm in diameter, 2) number of nodules ≤ 3, 3) absence of tumor thrombus in the portal vein, 4) absence of extrahepatic metastasis, 5) Child-Pugh class A or B, 6) prothrombintime ratio ≥ 50%, 7) platelet counts ≥ 50,000 cell/mm^3, 8) depicted nodules with ultrasound (US).

The baseline characteristics of the 75 patients were shown in Table 1. Of the 75 patients, 57 were men and 18 women, whose age ranged from 44 years to 83 years (median, 69 years, mean, 68 years). 69 patients (92.0%) had a solitary nodule and 6 patients (8.0%) had two nodules. The size of total 81 nodules ranged 5 - 30 mm (median, 15 mm). Of 81 nodules, 69 nodules (85.2%) were <2 cm in diameter and 12 nodules (14.8%) were ≥2 cm. Of the 75 patients, 69 patients were classified into Child-Pugh A and eight patients into Child-Pugh B before RFA. Although most patients were believed to be candidates for repeat hepatectomy, surgeons and radiologists in our hospital had consequence that RFA is a first-line treatment for an initial recurrent HCC.

The diagnosis of recurrent HCC was made on the basis of imaging findings: newly presenting tumors at follow-up dynamic multi-detector CT, or dynamic EOB-MRI, and abdominal US after hepatectomy, and characteristic enhancement patterns on the early phase of dynamic multi-detector CT, dynamic EOB-MRI [10], or contrast enhanced US using perfluorocarbon microbubbles (Sonazoid, Daiichi-Sankyo, Tokyo, Japan) [11] in 77 nodules, and confirmed by percutaneous needle biopsy in 4 nodules. Intrahepatic recurrent HCC were diagnosed from 3 to 150 months after hepatectomy (mean, 28.9 months; median, 19.5 months).

Table 1. Patients' background and tumor characteristics.

Demographic characteristic	Value
No. of patients	75
Age (y), mean ± SD	68.0 ± 9.0
<70	39
≥70	36
Gender	
Male	57
Female	18
Cause of liver cirrhosis	
Hepatitis C virus	44
Other	31
Clinical characteristics at the time of initial hepatectomy	
Child-Pugh class	
A	73
B	1
Maximum tumor diameter(cm)	

Continued

<5	46
≥5	14
Tumor number	
Single	61
Multiple	1
Hepatectomy type	
≤Lobectomy	69
>Lobectomy	6
Microvascular invasion	
Positive	21
Negative	41
Degree of differentiation	
Well or moderate	43
Poorly	15
AFP level (ng/mL)	
<100	53
≥100	15
PIVKA-2 level (ng/mL)	
<100	22
≥100	32
Clinical characteristics before RFA	
Child-Pugh class	
A	67
B	8
Maximum tumor diameter (mm)	
<20	69
≥20	12
AFP level (ng/ml)	
<100	60
≥100	13
PIVKA-2 level (ng/mL)	
<100	55
≥100	18
recurrence interval after hepatectomy (y)	
<1	20
≥1	55

2.1. RFA Procedures

An internally cooled electrode system (Cool-tip RF Ablation System, Covidien, MA) [12] was used for 69 patients. This system consists of a 480-kHz generator; a 20- or 15-cm-long, 17-gauge cooled-tip radiofrequency electrode with a 2- to 3-cm-long exposed metallic tip; and a dispersive pad applied to the patient's skin. Grounding was achieved by attaching a dispersive pad to each of the patient's thighs. RF 2000 system (Radio Therapeutics Corporation, Mountain View, CA, USA) [12] was used for 6 patients. This system consists of a 460-kHz generator; a LeVeen 15-gauge monopolar array electrode with 8 or 10 expandable electrode tines with 2- or 3-cm diameter; and a dispersive pad applied to the patient's skin. Grounding was achieved by attaching a dispersive pad to each of the patient's thighs. Three authors (K.S., T.S., and R.I.), who have 8, 29, and 10 years of experience each in interventional radiology, performed RFA under US guidance. 54 nodules were treated under guidance of B-mode US, and 27 nodules treated under guidance of Sonazoid-CE-US [11].

On contrast harmonic sonography using Sonazoid (Sonazoid-CEUS), early vascular imaging which can show the perfusion features of the microvascular bed of the liver parenchyma and tumor, and late liver parenchymal imaging (Kupffer imaging) can be obtained. After Sonazoid-CEUS was performed, a radiofrequency electrode was introduced into a HCC nodule under guidance of Kupffer imaging.

Combined RFA and TACE [13] [14] were performed in 22 nodules of 21 patients. First TACE was performed: introducing a microcatheter into a feeding hepatic artery segmentally or sub-segmentally after diagnostic celiac and superior mesenteric arteriography. Then, emulsion of 20 - 40 mg doxorubicin (Epirubicin, Tokyo) and 2 - 4 ml Lipiodol (iodized-oil, Tokyo) was injected via the microcatheter followed by injection of gelatin particles (Gelfoam or Gelpart, Tokyo). Then, RFA was performed within 1 week later.

2.2. Follow-Up

Dynamic CT was performed within a week after RFA to evaluate therapeutic effectiveness [15]. Residual unablated lesions were defined as irregular peripheral-enhancing foci in the ablation zones. The residual unablated lesions were treated with additional RFA. When a non-enhancing area larger than the nodule was noted at post-treatment dynamic CT, we diagnosed the therapeutic efficacy as complete.

The patients were followed up in the clinic at 2- or 3-month intervals. At each follow-up visit, blood tests, including those to measure levels of serum a-fetoprotein and prothrombin induced by vitamin K absence or agonist II (PIVKA-II), were performed. Dynamic CT or dynamic EOB-MRI was performed at 3-month intervals. Local recurrence was defined as a newly appearing enhancing lesion in or near the treated nodule [15]. The occurrence of new lesions in the liver was also evaluated with follow-up dynamic CT or dynamic EOB-MRI. Two

authors (M.K. and T.K.) assessed these findings. Local recurrence or occurrence of new lesions in the liver was treated with RFA, TACE, or hepatic resection. RFA was performed when three or fewer nodules 3 cm or less in diameter were detected, and TACE was performed if the largest nodule detected was larger than 3 cm or when there were more than three nodules, regardless of their size.

2.3. Evaluation

Overall survivals were defined as the interval between the first RFA and the death or the last visit to the outpatient clinic until May 2015. Local recurrence rates were defined as the interval between the first RFA and diagnosis of local recurrence, the last visit to the outpatient clinic, or the death until May 2015. Event-free survival rates were defined as the interval between the first RFA and diagnosis of local recurrence or occurrence of new HCC in the liver, distant metastasis, the last visit to the outpatient clinic, or the death until May 2015. The follow-up periods after RFA for recurrent HCC ranged 3 month to 151 months (median, 55 months, mean, 58.9 months).

The prognostic factors of the baseline characteristics before RFA included patient age (≥70 years or <70 years), gender, Child-Pugh classes (A or B), serum AFP level (>100 ng/mL or <100 ng/mL), PIVKA-2 (>100 ng/mL or <100 ng/mL), nodular size, ablated margin (<5 mm or ≥5 mm), combined TACE or not, local recurrence (present or absent) were assessed with the Cox proportional hazard models. We also evaluated the prognostic factors of the clinico-patho- logic variables related to hepatectomy. These were Child-Pugh classes (A or B), serum AFP level (≥100 ng/mL or <100 ng/mL), PIVKA-II (≥100 ng/mL or <100 ng/mL), and resected tumor size (≥5 cm or <5 cm) before hepatectomy. The factors during and after hepatectomy included positive microvascular invasion or negative, degree of the differentiation of HCC (poorly or moderate/well-differentiated), and recurrence interval after hepatectomy (≥1 year or <1 year). These were assessed by using the Cox proportional hazard models.

2.4. Statistical Analysis

SPSS was used. A P value < 0.05 was considered to indicate a significant difference. Data processing and analysis were performed with commercially available software (SPSS for Windows, version 13.0; SPSS, Chicago, IL, USA).

3. Results

A total of 81 RFA sessions were performed for 81 HCC nodules of 75 patients. Of 81 nodules, 78 were completely ablated with an initial RFA session (**Figure 1**): primary therapeutic effectiveness, 96.3% (78/81 nodules). In the other three nodules, the second RFA session was added for the residual enhanced foci and complete therapeutic effectiveness was obtained. In all the 81 nodules secondary effectiveness was 100% (81/81 nodules). Of the 81 nodules, 61 nodules (75.3%)

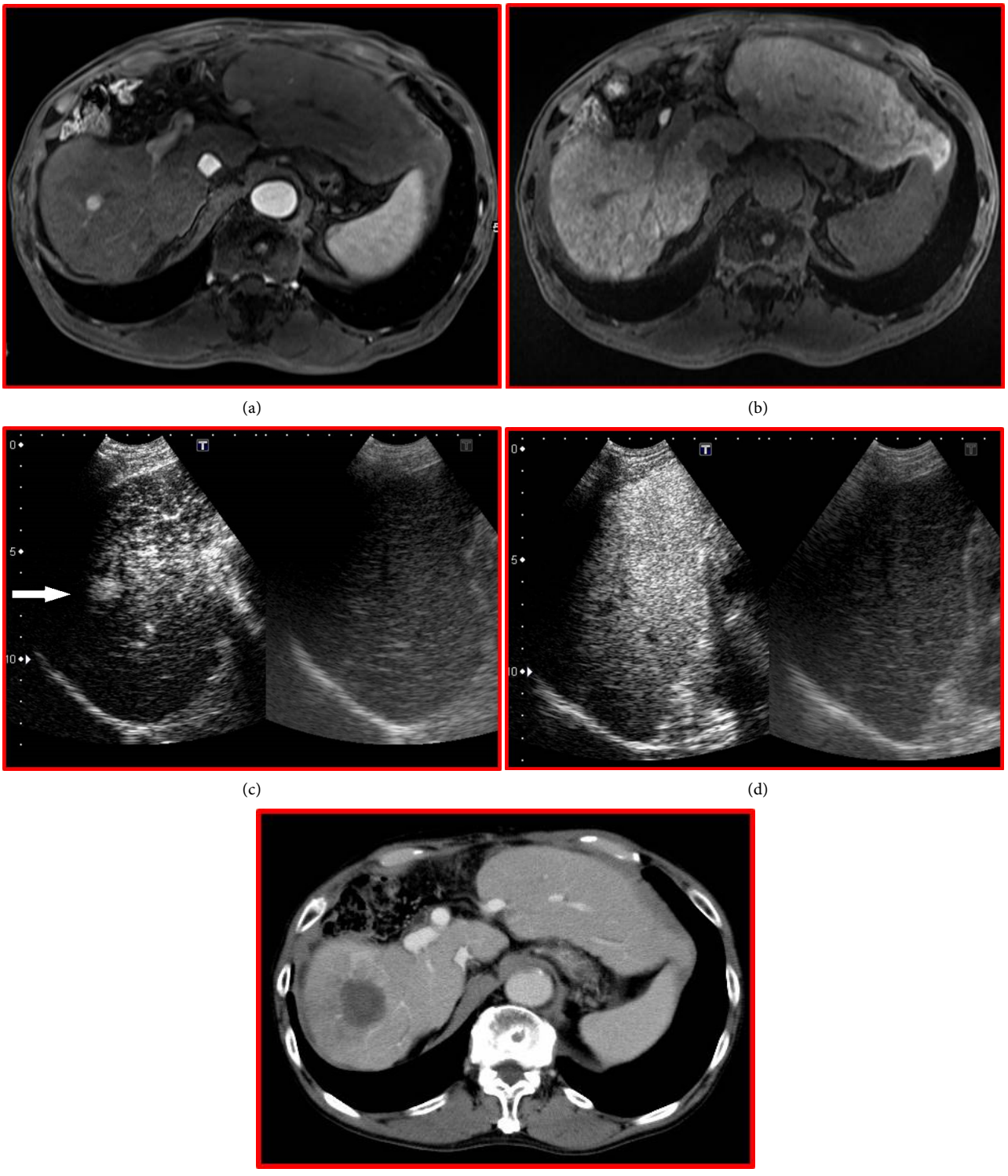

Figure 1. 75-year-old man with HCV-cirrhosis, who had undergone central bisegmentectomy 1.5 year ago, developed a recurrent HCC. (a) Early-phase dynamic EOB-MRI shows an enhanced nodule sized 1.7 cm in segment 7. (b) Hepatobiliary phase at dynamic EOB-MRI shows a low intense nodule in segment 7. (c) The nodule was invisible with B-mode US, but vascular imaging of Sonazoid-CEUS depicted a highechoic nodule (an arrow). (d) The nodule was noted as low echoic, and RFA was performed under Kupffer imaging. (e) Dynamic CT obtained 3days after RFA showed a low dense area larger than the recurrent nodule. The nodule was completely ablated.

had the circumferential ablative margin with >5 mm (ideal circumferential ablative margin) and in 20 nodules (24.7%) the circumferential ablative margin was <5 mm.

During follow-up periods after RFA (3 to 151 months, median, 55 months), local recurrence was noted in 10 nodules of 10 patients (10/81 nodules = 12.3%). The rates of local recurrence were 1-yr, 3-yr, 5-yr, and 8-yr were 7.6%, 12.0%, 12.0%, and 12.0%, respectively. During the follow-up periods, 36 patients were alive and 39 died. The cumulative overall survival rates of 1-yr, 3-yr, 5-yr, and 10-yr were 97.3%, 79.1%, 56.6%, and 32.2%, respectively (**Figure 2**). The median survival time was 55 months. Of the 75 patients, 66 patients developed new HCC in the liver, lung metastasis in 5 patients, bone metastasis in 3 patients, lymph node metastasis in 2 patients. Nine patients were no recurrent HCC in the liver or no distant metastasis. The cumulative disease-free survival rates of 1-yr, 3-yr, and 5-yr were 42.7%, 15.8%, and 12.6%, respectively (**Figure 3**). The median disease-free survival time was 12.3 months. There were significant differences among the subgroups divided by the Child-Pugh class (A or B) before RFA (p = 0.007) as to overall survival rates, and the subgroups divided by the Child-Pugh class (A or B) in clinico-pathologic variables related to hepatectomy as to disease-free survival rates (p = 0.004) (**Table 2**). There were no significant differences among the subgroups that were divided by other variables.

4. Discussion

Current imaging modalities, including dynamic multi-detector CT, dynamic EOB-MRI, or Sonazoid-contrast-enhanced US have high sensitivity for diagnosing HCC [16] [17] [18]. Especially patients with prior hepatectomy for HCC are high-risk groups of occurring HCC in the remaining liver [3] [4] [5]. In our

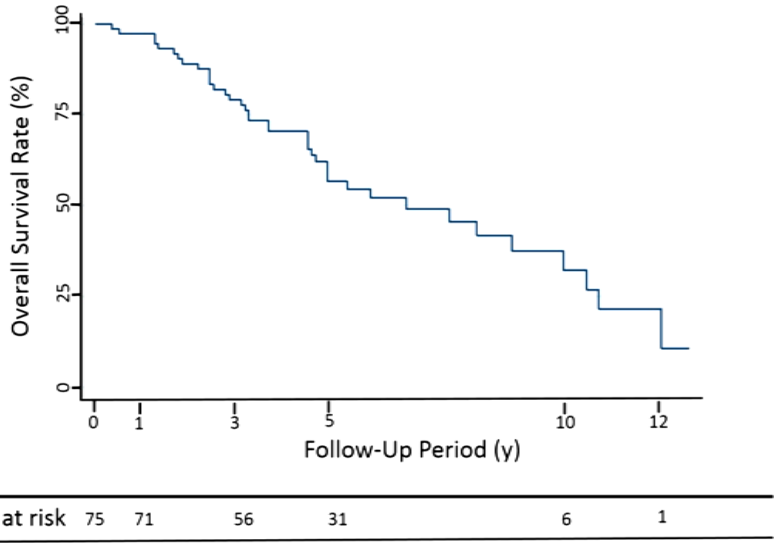

Figure 2. Graphs shows overall survival rates in patients with recurrent HCC nodules treated with RFA (n = 75). The overall survival rates of 1-yr, 3-yr, 5-yr, and 10-yr were 97.3%, 79.1%, 56.6%, and 32.2%, respectively.

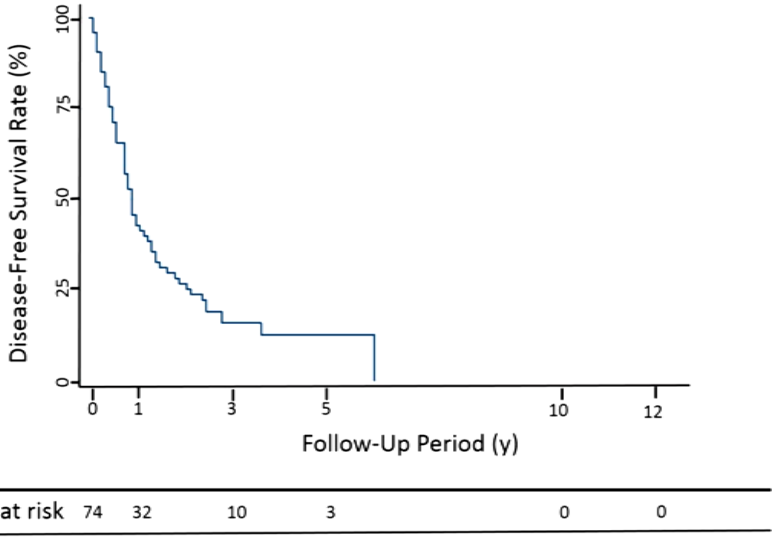

Figure 3. Graphs shows disease-free survival rates in patients with recurrent HCC nodules treated with RFA (n = 75). The disease-free survival rates of 1-yr, 3-yr, and 5-yr were 42.7%, 15.8%, and 12.6%, respectively.

Table 2. Prognostic factors of overall survival rate and disease-free survival rates.

Overall survival rate		Disease-free survival rates	
The baseline characteristics before RFA	*P* value	The baseline characteristics before RFA	*P* value
Age, younger (<70): older (≥70)	NS (0.748)	Age, younger (<70): older (≥70)	NS (0.233)
Gender, male: female	NS (0.843)	Gender, male: female	NS (0.650)
Child-Pugh, Class A: Class B	0.007	Child-Pugh, Class A: Class B	NS (0.163)
Serum AFP level, <100 ng/mL: ≥100 ng/mL	NS (0.551)	Serum AFP level, <100 ng/mL: ≥100 ng/mL	NS (0.390)
Serum PIVKA-2 level, <100 ng/mL: ≥100 ng/mL	NS (0.092)	Serum PIVKA-2 level, <100 ng/mL: ≥100 ng/mL	NS (0.088)
The clinic-pathologic characteristics related to RFA		The clinic-pathologic characteristics related to RFA	
Tumor size, <20 mm: ≥20 mm	NS (0.962)	Tumor size, <20 mm: ≥20 mm	NS (0.640)
Ablated margin, <5 mm: ≥5 mm	NS (0.087)	Ablated margin, <5 mm: ≥5 mm	NS (0.616)
RFA alone: combined RFA and TACE	NS (0.097)	RFA alone: Combined RFA and TACE	NS (0.950)
Local recurrence	NS (0.92)	Local recurrence	NS (0.071)
The characteristics before hepatectomy		The characteristics before hepatectomy	
Child-Pugh, Class A: Class B	NS (0.286)	Child-Pugh, Class A: Class B	0.004
Serum AFP level, <100 ng/mL: ≥100 ng/mL	NS (0.704)	Serum AFP level, <100 ng/mL: ≥100 ng/mL	NS (0.348)
Serum PIVKA-2 level, <100 ng/mL: ≥100 ng/mL	NS (0.775)	Serum PIVKA-2 level, <100 ng/mL: ≥100 ng/mL	NS (0.235)
Resected tumor size, <5 cm: ≥5 cm	NS (0.950)	Resected tumor size, <5 cm: ≥5 cm	NS (0.879)
The characteristics after hepatectomy		The characteristics after hepatectomy	
Microvascular invasion, positive: negative	NS (0.097)	Microvascular invasion, positive: negative	NS (0.521)
Differentiation, poorly: moderate/well	NS (0.852)	Differentiation, poorly: moderate/well	NS (0.743)
Recurrence interval, <1 year: ≥1 year	NS (0.468)	Recurrence interval, <1 year: ≥1 year	NS (0.227)

study, postoperative follow-up dynamic CT or dynamic EOB-MRI was frequently performed at 3-month intervals in all patients. So early diagnosis of recurrent HCC could be performed. The size of the 81 recurrent HCCs ranged 5 - 30 mm (median, 15 mm), and 69 of 81 nodules (85.2%) were ≤2 cm in diameter.

For treatment of native HCC ≤ 2 cm in diameter, overall survival rates of patients treated with RFA are comparable to those of hepatectomy [19] [20]. There have been some reports comparing the outcomes of repeated hepatectomy and RFA for recurrent HCC after hepatectomy [21] [22] [23] [24]. Chan AC *et al.* [21] compared the efficacy of salvage liver transplantation, repeated hepatic resection and RFA in the treatment of intrahepatic HCC recurrence after hepatectomy; salvage liver transplantation and repeated hepatic resection showed comparable survival outcomes, but both treatments were significantly better survival outcomes than RFA. However, Song KD *et al.* [22] described that RFA and repeated hepatectomy attained similar survival benefits in the management of recurrent HCC after hepatectomy. They compared the long-term outcomes of repeated hepatic resection and RFA for recurrent HCC by using propensity score matching. They showed that the overall survival rates at 1, 3, 5, and 8 years were 98.7%, 85.7%, 72.1%, and 68.6%, respectively, and the disease-free survival rates at 1, 3, and 5 years were 71.8%, 45.1%, and 39.4% in the RFA group. No statistical differences of overall survivals and disease-free survivals were noted between RFA and repeated hepatectomy groups.

However, the repeated hepatectomy would be technically more difficult, because of intra-abdominal adhesions caused by previous hepatic resections as well as new growth of intrahepatic vascular structures after previous hepatic resection, and there is a potential risk of postoperative hepatic failure after repeated hepatic resection in patients with limited hepatic function reserve [22]. On the other hand, RFA can be repeatedly performed for local recurrence after both RFA and new HCC appeared in the remaining liver. Moreover, RFA is less morbidity and mortality than hepatectomy. So, in our study RFA has been performed as a first-line treatment for the initial intrahepatic recurrence after hepatectomy, although most of the 75 patients would undergo repeated hepatectomy because of the good hepatic reserve. Our results of the cumulative overall survivals: 1-yr, 3-yr, 5-yr, and 10-yr, 97.3%, 79.1%, 56.6%, and 32.2% and disease-free survivals: 1-yr, 3-yr, and 5-yr, 42.7%, 15.8%, and 12.6%, respectively were comparable to those of the previous reports.

In two studies, long-term survival of patients with native HCC treated with percutaneous RFA as a first-line treatment depended upon the Child-Pugh class, serum AFP level, tumor size, and multiplicity of tumors [25] [26]. In the study of Choi D, *et al.* [15], high serum AFP level before RFA and resected tumor size at initial hepatectomy were independent significant predictive factors of long-term survival in patients with recurrent HCC after hepatectomy. Lu *et al.* [8] reported that the pre-ablation serum AFP level was the only prognostic predictor, and recurrence intervals after hepatectomy and tumor staging were not related to

survival. In our study, a prognostic factor affected to overall survivals was Child-Pugh classification (Child A or B) before RFA and that affected to event-free-survivals was Child-Pugh classification (Child A or B) before hepatectomy. Other factors, such as the gender and age etc. did not influence the prognosis.

Takaki *et al.* [26] showed that a single tumor at the time of initial hepatectomy and a low *a*-fetoprotein level (≤100 ng/mL) at recurrence were significantly favorable independent factors affecting overall and recurrence-free survival. Choi *et al.* [15] described a lower serum AFP level (≤100 ng/mL) before RFA or with small resected tumors (≤5 cm) demonstrated better survival results [15]. In our study the most patients had small (median, 15 mm), single recurrent tumor, so tumor size and multiplicity of tumors would not be included into prognostic factors.

This study has several important limitations. First, this was a single-arm retrospective study. RFA was not performed for HCC nodules undetected at US. Moreover we should compare the outcomes between RFA and repeated hepatectomy.

5. Conclusion

In conclusion, RFA was an effective, useful therapeutic option for treatment of recurrent HCC after hepatectomy. Child-Pugh Class (A or B) before RFA and Child-Pugh classification (Child A or B) in clinico-pathologic variables related to hepatectomy were significant prognostic predictors of long-term survival. The use of RFA was recommended for the treatment of recurrent tumors after hepatic resection.

References

[1] Forner, A., Llovet, J.M. and Bruix, J. (2012) Hepatocellular Carcinoma. *Lancet*, **379**, 1245-1255. https://doi.org/10.1016/S0140-6736(11)61347-0

[2] Sugimachi, K., Maehara, S., Tanaka, S., Shimada, M. and Sugimachi, K. (2001) Repeat Hepatectomy Is the Most Useful Treatment for Recurrent Hepatocellular Carcinoma. *Journal of Hepato-Biliary-Pancreatic Surgery*, **8**, 410-416. https://doi.org/10.1007/s005340100002

[3] Matsuda, M., Fujii, H., Kono, H. and Matsumoto, Y. (2001) Surgical Treatment of Recurrent Hepatocellular Carcinoma Based on the Mode of Recurrence: Repeat Hepatic Resection or Ablation Are Good Choices for Patients with Recurrent Multicentric cancer. *Journal of Hepato-Biliary-Pancreatic Surgery*, **8**, 353-359. https://doi.org/10.1007/s005340170008

[4] Nicoli, N., Casaril, A., Marchiori, L., Mangiante, G. and Hasheminia, A.R. (2001) Treatment of Recurrent Hepatocellular Carcinoma by Radiofrequency Thermal Ablation. *Journal of Hepato-Biliary-Pancreatic Surgery*, **8**, 417-421. https://doi.org/10.1007/s005340100003

[5] Elias, D., De Baere, T., Smayra, T., Ouellet, J.F., Roche, A. and Lasser, P. (2002) Percutaneous Radiofrequency Thermoablation as an Alternative to Surgery for Treatment of Liver Tumour Recurrence after Hepatectomy. *The British Journal of*

Surgery, **89**, 752-756. https://doi.org/10.1046/j.1365-2168.2002.02081.x

[6] Choi, J.W., Park, J.Y., Ahn, S.H., Yoon, K.T., Ko, H.K., Lee Do, Y., *et al.* (2009) Efficacy and Safety of Transarterial Chemoembolization in Recurrent Hepatocellular Carcinoma after Curative Surgical Resection. *American Journal of Clinical Oncology*, **32**, 564-569. https://doi.org/10.1097/COC.0b013e3181967da0

[7] Choi, D., Lim, H.K., Kim, M.J., Lee, S.H., Kim, S.H., Lee, W.J., *et al.* (2004) Recurrent Hepatocellular Carcinoma: Percutaneous Radiofrequency Ablation after Hepatectomy. *Radiology*, **230**, 135-141. https://doi.org/10.1148/radiol.2301021182

[8] Lu, M.D., Yin, X.Y., Xie, X.Y., Xu, H.X., Xu, Z.F., Liu, G.J., *et al.* (2005) Percutaneous Thermal Ablation for Recurrent Hepatocellular Carcinoma after Hepatectomy. *The British Journal of Surgery*, **92**, 1393-1398. https://doi.org/10.1002/bjs.5102

[9] Yang, W., Chen, M.H., Yin, S.S., Yan, K., Gao, W., Wang, Y.B., *et al.* (2006) Radiofrequency Ablation of Recurrent Hepatocellular Carcinoma after Hepatectomy: Therapeutic Efficacy on Early- and Late-Phase Recurrence. *American Journal of Roentgenology*, **186**, S275-S283. https://doi.org/10.2214/AJR.04.1573

[10] Kudo, M., Izumi, N., Kokudo, N., Matsui, O., Sakamoto, M., Nakashima, O., *et al.* (2011) Management of Hepatocellular Carcinoma in Japan: Consensus-Based Clinical Practice Guidelines Proposed by the Japan Society of Hepatology (JSH) 2010 Updated Version. *Digestive Diseases*, **29**, 339-364. https://doi.org/10.1159/000327577

[11] Minami, Y., Kudo, M., Chung, H., Kawasaki, T., Yagyu, Y., Shimono, T., *et al.* (2007) Contrast Harmonic Sonography-Guided Radiofrequency Ablation Therapy versus B-Mode Sonography in Hepatocellular Carcinoma: Prospective Randomized Controlled Trial. *American Journal of Roentgenology*, **188**, 489-494. https://doi.org/10.2214/AJR.05.1286

[12] Shibata, T., Shibata, T., Maetani, Y., Isoda, H. and Hiraoka, M. (2006) Radiofrequency Ablation for Small Hepatocellular Carcinoma: Prospective Comparison of Internally Cooled Electrode and Expandable Electrode. *Radiology*, **238**, 346-353. https://doi.org/10.1148/radiol.2381041848

[13] Yamakado, K., Nakatsuka, A., Takaki, H., Yokoi, H., Usui, M., Sakurai, H., *et al.* (2008) Early-Stage Hepatocellular Carcinoma: Radiofrequency Ablation Combined with Chemoembolization versus Hepatectomy. *Radiology*, **247**, 260-266. https://doi.org/10.1148/radiol.2471070818

[14] Takuma, Y., Takabatake, H., Morimoto, Y., Toshikuni, N., Kayahara, T., Makino, Y., *et al.* (2013) Comparison of Combined Transcatheter Arterial Chemoembolization and Radiofrequency Ablation with Surgical Resection by Using Propensity Score Matching in Patients with Hepatocellular Carcinoma within Milan Criteria. *Radiology*, **269**, 927-937. https://doi.org/10.1148/radiol.13130387

[15] Choi, D., Lim, H.K., Rhim, H., Kim, Y.S., Yoo, B.C., Paik, S.W., *et al.* (2007) Percutaneous Radiofrequency Ablation for Recurrent Hepatocellular Carcinoma after Hepatectomy: Long-Term Results and Prognostic Factors. *Annals of Surgical Oncology*, **14**, 2319-2329. https://doi.org/10.1245/s10434-006-9220-8

[16] Huppertz, A., Haraida, S., Kraus, A., Zech, C.J., Scheidler, J., Breuer, J., *et al.* (2005) Enhancement of Focal Liver Lesions at Gadoxetic Acid-Enhanced MR Imaging: Correlation with Histopathologic Findings and Spiral CT—Initial Observations. *Radiology*, **234**, 468-478. https://doi.org/10.1148/radiol.2342040278

[17] Kudo, M. (2011) Diagnostic Imaging of Hepatocellular Carcinoma: Recent Progress. *Oncology*, **81**, 73-85. https://doi.org/10.1159/000333265

[18] Bruix, J. and Sherman, M. (2011) Management of Hepatocellular Carcinoma: An

Update. *Hepatology*, **53**, 1020-1022. https://doi.org/10.1002/hep.24199

[19] Cho, Y.K., Kim, J.K., Kim, W.T. and Chung, J.W. (2010) Hepatic Resection versus Radiofrequency Ablation for Very Early Stage Hepatocellular Carcinoma: A Markov Model Analysis. *Hepatology*, **51**, 1284-1290. https://doi.org/10.1002/hep.23466

[20] Wang, J.-H., Wang, C.-C., Hung, C.-H., Chen, C.-L. and Lu, S.-N. (2012) Survival Comparison between Surgical Resection and Radiofrequency Ablation for Patients in BCLC Very Early/Early Stage Hepatocellular Carcinoma. *Journal of Hepatology*, **56**, 412-418.

[21] Chan, A.C., Chan, S.C., Chok, K.S., Cheung, T.T., Chiu, D.W., Poon, R.T., *et al*. (2013) Treatment Strategy for Recurrent Hepatocellular Carcinoma: Salvage Transplantation, Repeated Resection, or Radiofrequency Ablation? *Liver Transplantation*, **19**, 411-419. https://doi.org/10.1002/lt.23605

[22] Song, K.D., Lim, H.K., Rhim, H., Lee, M.W., Kim, Y.S., Lee, W.J., *et al*. (2015) Repeated Hepatic Resection versus Radiofrequency Ablation for Recurrent Hepatocellular Carcinoma after Hepatic Resection: A Propensity Score Matching Study. *Radiology*, **275**, 599-608. https://doi.org/10.1148/radiol.14141568

[23] Joliat, G.R., Allemann, P., Labgaa, I., Demartines, N. and Halkic, N. (2017) Treatment and Outcomes of Recurrent Hepatocellular Carcinomas. *Langenbeck's Archives of Surgery*, **402**, 737-744. https://doi.org/10.1007/s00423-017-1582-9

[24] Gavriilidis, P., Askari, A. and Azoulay, D. (2017) Survival Following Redo Hepatectomy vs. Radiofrequency Ablation for Recurrent Hepatocellular Carcinoma: A Systematic Review and Meta-Analysis. *HPB*, **19**, 3-9.

[25] Tateishi, R., Shiina, S., Teratani, T., Obi, S., Sato, S., Koike, Y., *et al*. (2005) Percutaneous Radiofrequency Ablation for Hepatocellular Carcinoma. An Analysis of 1000 Cases. *Cancer*, **103**, 1201-1209. https://doi.org/10.1002/cncr.20892

[26] Takaki, H., Yamakado, K., Sakurai, H., Nakatsuka, A., Shiraki, K., Isaji, S., *et al*. (2011) Radiofrequency Ablation Combined with Chemoembolization: Treatment of Recurrent Hepatocellular Carcinomas after Hepatectomy. *American Journal of Roentgenology*, **197**, 488-494. https://doi.org/10.2214/AJR.10.4933