TABLE 1 Baseline characteristics and operative data on patients who underwent hepatectomy: data are reported for whole study and for the matched study population after propensity score analysis

	Overall series		*P* value	Propensity-matched series		*P* value
	IFN (+) $n = 43$	IFN (−) $n = 76$		Peg-IFN (+) $n = 38$	IFN (−) $n = 38$	
Age (years)	65 (53–78)	71 (48–83)	0.0003	65.5 (53–75)	69 (51–80)	0.2
Sex (male/female)	27/16	47/29	0.918	23/15	25/13	0.634
Preoperative IFN	24 (55.8%)	29 (38.1%)	0.06	20 (52.6%)	14 (36.8%)	0.16
HCV genotype			0.876			0.6
1b	34	61		29	27	
2b	9	15		9	11	
Diabetes mellitus	11 (25.6%)	22 (28.9%)	0.856	11 (28.9%)	13 (34.2%)	0.621
ECOG PS			0.831			0.644
0	39	68		36	35	
1	4	8		2	3	
Platelet ($104/mm^3$)	10.3 (3.3–26.6)	10.3 (3.8–40.3)	0.381	9.75 (3.3–21.5)	11.2 (3.8–40.3)	0.454
T-Bil (mg/dl)	0.7 (0.3–1.4)	0.8 (0.3–1.7)	0.292	0.7 (0.4–1.4)	0.7 (0.3–1.7)	0.798
AST (IU/l)	42 (18–121)	48 (16–150)	0.152	43.5 (18–127)	41.5 (6–150)	0.567
ALT (IU/l)	38 (13–127)	41.5 (10–196)	0.987	40.5 (11–127)	37.5 (10–196)	0.226
Albumin (g/dl)	3.8 (2.8–5.2)	3.8 (2.5–4.9)	0.215	3.8 (2.8–5.2)	3.8 (2.5–4.5)	0.469
ICGR 15 (%)	17.9 (7.4–77.4)	18.7 (4.6–50.5)	0.734	17.65 (7.4–40.0)	17.55 (4.6–40.0)	0.561
AFP (ng/ml)	11.6 (0.5–3405)	27.6 (0.5–36572)	0.176	13.95 (0.5–3405)	22.9 (0.5–513)	0.635
Child–Pugh grade			0.665			0.556
A	41 (95.3%)	69 (90.8%)		37 (97.4%)	36 (94.7%)	
B	2 (4.7%)	7 (9.2%)		1 (2.6%)	2 (5.3%)	
Hepatic resection			0.322			0.373
Hr0	20 (46.5%)	49 (64.5%)		18 (47.4%)	23 (60.5%)	
HrS	13 (30.2%)	18 (23.7%)		12 (31.6%)	9 (23.7%)	
Hr1	3 (7.0%)	4 (5.3%)		2 (5.3%)	3 (7.9%)	
Hr2	7 (16.3%)	5 (6.6%)		6 (15.8%)	2 (5.3%)	
Hr3	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Operation time (min)	260 (128–623)	242 (90–580)	0.0514	257 (128–623)	247.5 (90–580)	0.18
Blood loss (ml)	200 (20–1900)	225 (10–960)	0.996	210 (20–1900)	210 (10–960)	0.803
Postoperative complications			0.933			0.798
IIIa	4	6		2	2	
IIIb	1	1		1	1	
IVa	1	1		1	0	
Stage			0.315			0.293
I	14 (32.6%)	19 (25.0%)		13 (34.2%)	9 (23.7%)	
II	18 (41.9%)	44 (57.9%)		15 (39.5%)	23 (60.5%)	
III	9 (20.9%)	12 (15.8%)		9 (23.7%)	6 (15.8%)	
IV-A	2 (4.7%)	1 (1.3%)		1 (2.6%)	0 (0.0%)	
Single tumor	28 (65.1%)	57 (75.0%)	0.252	25 (65.8%)	29 (76.3%)	0.312
Tumor size			0.712			0.589
≥3 cm	15 (34.9%)	24 (31.6%)		10 (26.3%)	8 (21.1%)	
<3 cm	28 (65.1%)	52 (68.4%)		28 (73.7%)	30 (78.9%)	
Vascular invasion	4 (9.3%)	3 (3.9%)	0.233	3 (7.9%)	0 (0.0%)	0.239

Continuous variables expressed as median (range)

Hepatic resection and stage were according to General Rules for the Clinical and pathological Study of Primary Liver Cancer, by Liver cancer Study Group of Japan, 5th edition, Kanehara Co., Ltd

Hr0: limited resection, HrS: segmentectomy, Hr1: sectionectomy, Hr2: hemihepatectomy, Hr3: more than hemihepatectomy

T-Bil total bilirubin, *PS* performance status, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ICGR 15* indocyanine green retention rate at 15 min, *AFP* alpha-fetoprotein,

did not receive IFN therapy was 3.8 (1.2–6.9) and 3.5 (1.3–6.8) years, respectively. In the matched study groups, the 3- and 5-year overall survival rates of patients who received peg-IFN therapy after hepatic resection were significantly higher than those of patients who did not receive IFN therapy ($P = 0.00135$) (Fig. 1c). However, there was no significant difference in disease-free survival between the two matched groups ($P = 0.886$) (Fig. 1d).

In the matched 38 patients of the peg-IFN group, peg-IFN therapy was initiated at a median of 4.3 (0.9–9.6) months after hepatic resection. Thirty-one of 38 HCC patients began peg-IFN therapy within 6 months after hepatectomy. Seven patients required more than 6 months to commence peg-IFN therapy. Two patients required a longer time to recover platelet counts of more than 70,000/μl. Five patients required a longer time to decide to receive peg-IFN therapy. Sixteen (42.1%) of the matched 38 patients who received peg-IFN therapy after hepatectomy attained SVR. Among 16 patients who attained SVR, 10 patients received full-dose peg-IFN therapy without dose reduction, whereas 6 patients received a reduced dose of peg-IFN and/or RBV until completion of treatment. Nine patients discontinued peg-IFN therapy because of adverse events such as thrombocytopenia and neutropenia ($n = 2$), skin eruption ($n = 1$), depression ($n = 2$), and severe malaise ($n = 4$). Three patients discontinued peg-IFN therapy because of HCC recurrence. Adherence to peg-IFN therapy was 68.4% in this study. No life-threatening adverse events were observed, and none of the total 15 deaths in both sets of matched patients were related to the IFN treatment or to surgical procedures. The 3- and 5-year overall survival rates of patients ($n = 16$) who attained SVR after peg-IFN therapy were 100% and 100%, respectively; those of patients who did not attain SVR ($n = 22$) were 100 and 85.7%, respectively; and those of patients who did not receive IFN therapy were 76.6 and 50.6%, respectively. There was a statistically significant difference in overall survival among the three groups ($P = 0.005$) (Fig. 2a). However, there was no statistically significant difference in disease-free survival among the three groups ($P = 0.90$) (Fig. 2b).

Table 2 presents the patterns of cancer recurrence and the treatment details of the recurrences in both groups. Twenty-one (55.3%) of the patients who received peg-IFN therapy after hepatic resection and 17 (44.7%) of the patients who did not receive IFN therapy had HCC recurrences after hepatic resection. Regarding the pattern of recurrence, the proportion of patients who had multiple

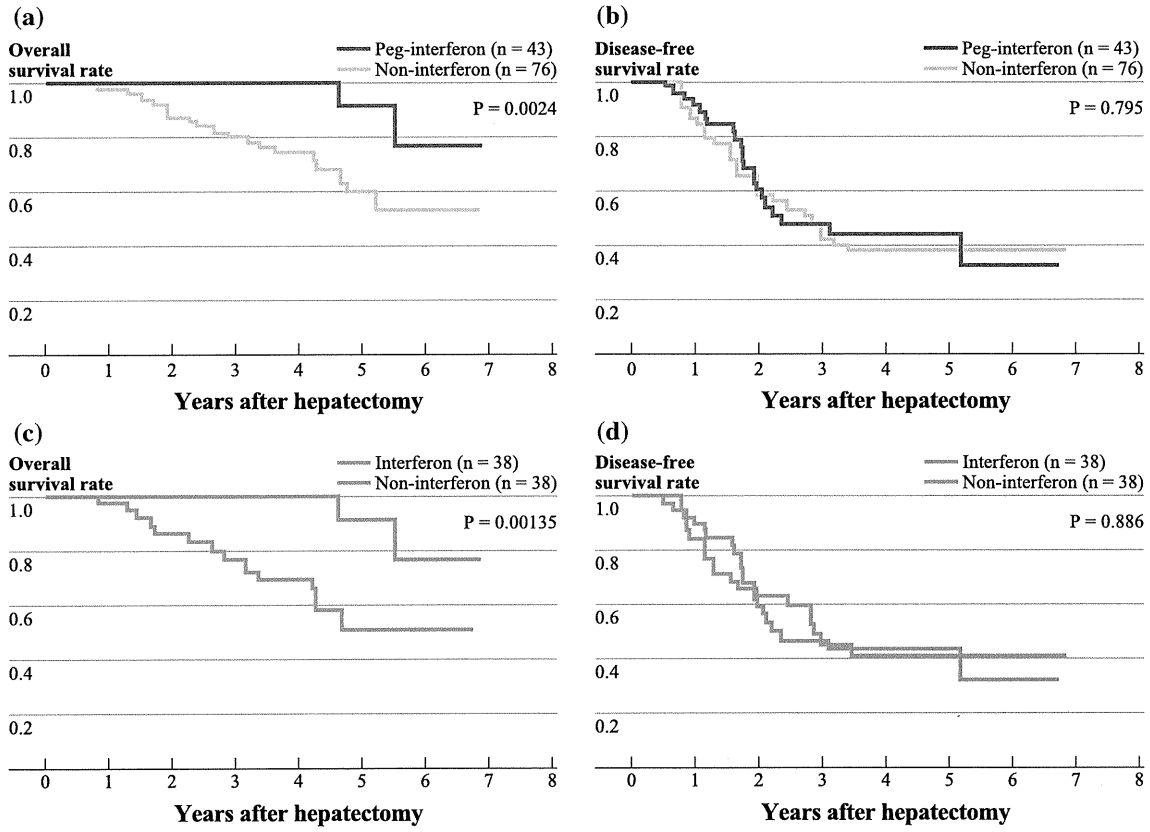

FIG. 1 Overall survival (**a**) and disease-free survival (**b**) of the entire study population of 175 patients with hepatitis C-related HCC with respect to IFN therapy after hepatic resection. Overall survival (**c**) and disease-free (**d**) survival of the matched study population of 76 patients with hepatitis C-related HCC with respect to IFN therapy after hepatic resection

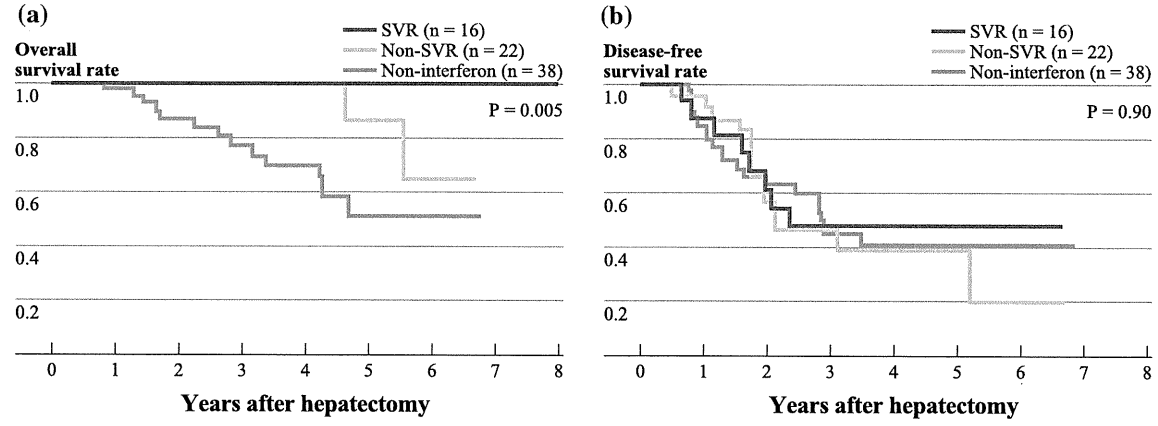

FIG. 2 Overall survival and disease-free survival of patients with hepatitis C-related HCC with respect to SVR after IFN therapy

intrahepatic recurrences (more than four nodules) was significantly lower in the peg-IFN group than in the non-IFN group ($P = 0.0047$). The proportion of patients in whom surgery or RFA was selected for treatment was significantly higher in the peg-IFN group than in the non-IFN group ($P = 0.0346$). Furthermore, regarding re-recurrence of HCC after treatment of the first-recurrent HCC, the 1-year disease-free survival rates of patients after treatment of the first-recurrent HCC was 48.5% in patients ($n = 21$) who received peg-IFN therapy and 12.5% in patients ($n = 17$) who did not receive IFN therapy. There was a statistically significant difference in disease-free survival between the two groups ($P = 0.0012$) (Fig. 3).

A comparison of results of the preoperative liver function test with those of postoperative 1-year liver function tests is presented in Table 3. In patients who received peg-IFN therapy, total bilirubin levels 1 year after surgery were significantly decreased compared with preoperative total bilirubin levels ($P = 0.018$), whereas in patients who did not receive IFN therapy, the total bilirubin level at 1 year after surgery was similar to the total bilirubin level before surgery ($P = 0.107$).

TABLE 2 Recurrence and treatments for recurrence after hepatic resection

	Peg-IFN (+) ($n = 38$)	IFN (−) ($n = 38$)	*P* value
HCC recurrence[a]: yes	21 (55.3%)	17 (44.7%)	0.359
Pattern of recurrence[b]			0.0047
Intrahepatic (single)	9 (42.9%)	8 (47.1%)	
Intrahepatic (2–3)	10 (47.6%)	1 (5.9%)	
Intrahepatic (multiple)	2 (9.5%)	8 (47.1%)	
Main modalities[b]			0.0346
Repeat hepatectomy	8 (38.1%)	2 (11.8%)	
RFA	8 (38.1%)	4 (23.5%)	
TACE	5 (23.8%)	11 (64.7%)	

peg-IFN pegylated interferon, *RFA* radiofrequency ablation, *TACE* transcatheter arterial chemoembolization

[a] Data expressed as number of patients (percentage of total patients)

[b] Data expressed as number of patients (percentage of patients who had a recurrence)

DISCUSSION

Our results revealed that peg-IFN therapy after hepatic resection improved the outcomes of HCV patients, although the interval of disease-free survival was not prolonged. Peg-IFN therapy after hepatectomy improved hepatic reserve function and suppressed multiple HCC recurrences (more than four nodules). Furthermore, re-recurrence after treatment of first-recurrent HCC after hepatic resection was significantly suppressed in the peg-IFN group compared with that in the non-IFN group. IFN has been reported to exert antitumor effects. IFN increases natural killer cell activity and exhibits antiangiogenic properties.[35,36] IFN has also been reported to be effective in eradicating HCV RNA

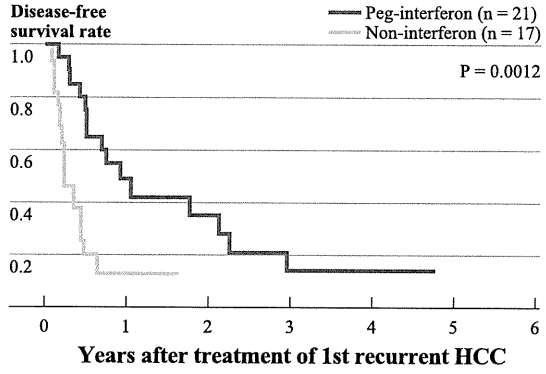

FIG. 3 Comparison of disease-free survival rate after treatment of first-recurrent HCC in patients who received peg-IFN therapy or in those who did not receive IFN therapy

TABLE 3 Comparison of preoperative liver function with 1-year liver function after hepatic resection

	Peg-IFN (+)		*P* value	IFN (−)		*P* value
	Preoperative	1 Year after surgery		Preoperative	1 Year after surgery	
T-Bil (mg/dl)	0.82 ± 0.29	0.71 ± 0.26	0.0189	0.81 ± 0.32	0.92 ± 0.35	0.107
AST (IU/l)	50.1 ± 24.1	45.8 ± 23.5	0.310	42.1 ± 18.9	56.1 ± 26.7	0.0110
ALT (IU/l)	51.3 ± 28.6	36.4 ± 22.8	0.00809	40.3 ± 24.3	49.7 ± 25.8	0.0918
Albumin (g/dl)	3.89 ± 0.80	3.99 ± 0.71	0.251	3.73 ± 0.45	3.75 ± 0.44	0.807

peg-IFN pegylated interferon, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase

from serum and hepatic tissue, thereby preventing deterioration of liver function in patients with HCV infection.[37] IFN prevents worsening of compensated cirrhosis.[18,37] Our results are compatible with those reported in those studies. In the peg-IFN group, most patients with HCC recurrence could undergo curative treatments such as repeat hepatectomy or RFA as a recurrence treatment, because the number of recurrent tumors was usually limited to three. IFN therapy appears to increase survival not only by improving residual liver function and increasing the possibility of radical treatment of recurrences but also by suppressing re-recurrence after the first recurrence of HCC.

The current study also revealed that the overall survival of patients with SVR was significantly better than that of patients without SVR. This result suggests that IFN prolongs the outcomes of patients with HCC after hepatic resection by causing remission of active hepatitis and eradication of HCV RNA in patients who attained SVR after hepatic resection.

In this study, to clarify the impact of peg-IFN therapy on outcomes of HCV-related HCC after hepatic resection, patients who received IFNs such as IFN-α or IFN-β were excluded. RCTs investigating adjuvant effects of IFN after resection or ablation of HCC were performed using IFN-α. Few studies have investigated the effects of peg-IFN plus RBV combination therapy on survival and recurrence after curative resection of HCC. Combination therapy with peg-IFN and RBV has recently been developed, and peg-IFN therapy has resulted in significantly higher SVR rates and better tolerability than treatment with IFN-α.[21,23] In our study, incidence of SVR after hepatic resection was 42.1%, which was higher than that in previous studies that reported an SVR rate of 0–10%.[12–14] The compliance of patients to peg-IFN therapy observed in the present study (68.4%) was higher than that reported elsewhere (approximately 40%).[14] This enhanced efficacy of the peg-IFN formulations might contribute to the prolonged survival of HCC patients after hepatic resection.

In this study, HCC patients who received peg-IFN therapy within 9 months after surgery were enrolled, and HCC patients who experienced recurrence of HCC within 9 months after hepatic resection were excluded from the non-IFN group, because these patients could lose the opportunity to receive IFN therapy for HCC recurrence on being assigned to the peg-IFN therapy group.

Before matching by using the propensity score, the clinical characteristics of the entire study population that can strongly influence outcomes differed significantly between the peg-IFN group and non-IFN group. The proportion of older patients was higher in the non-IFN group than in the peg-IFN group, whereas the proportion of patients who had longer operation times tended to be lower in the non-IFN group than in the peg-IFN group. To overcome bias due to the different distribution of the severity of liver function impairment between the two groups, a one-to-one match was created using propensity score analysis. After matching by propensity score, prognostic variables were appropriately handled, and there was no significant difference in prognostic factors between the two matched groups. This study had a limitation related to the small sample size after propensity score matching. To overcome this, further examination with larger sample sizes is necessary, and the potential efficacy of peg-IFN therapy must be validated in larger prospective RCTs.

CONCLUSIONS

Several previous RCTs investigating the effects of IFN on survival and tumor recurrence after hepatic resection were inconclusive. However, in the current study, peg-IFN therapy following hepatic resection improved the survival rates of hepatectomized patients with HCV-related HCC. The results of this study suggest that peg-IFN therapy is effective as an adjuvant chemopreventive agent after hepatic resection in patients with HCV-related HCC.

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CONFLICT OF INTEREST The authors have no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements) that might pose a conflict of interest related to the submitted manuscript.

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Treatment Strategy for Early Hepatocellular Carcinomas: Comparison of Radiofrequency Ablation With or Without Transcatheter Arterial Chemoembolization and Surgical Resection

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Background: The preferred choice between surgical treatment and radiofrequency ablation (RFA) for the treatment of small resectable hepatocelluar carcinoma (HCC) has become a subject for debate.
Methods: We compared the results of hepatic resection (n = 199) with those of RFA (n = 87), of which 69 patients were treated with transcatheter arterial chemoembolization followed by RFA, for 286 patients with 3 or fewer nodules, none of which exceeded 3 cm in diameter at Hiroshima University Hospital.
Results: In subgroup analysis of single HCC with tumor size exceeding 2 cm in Child-Pugh class A, the disease-free survival time was significantly longer in the surgical resection group than in the RFA group ($P = 0.048$). In the subgroups of a single and multiple HCC with tumor size $\leq$2 cm in Child-Pugh class A, the overall and disease-free survival rates were almost the same for the surgical resection and RFA groups ($P = 0.46$ and 0.58, respectively, in single HCC, and $P = 0.98$ and 0.98, respectively, in multiple HCC).
Conclusion: Surgical resection may provide better long-term disease-free survival than RFA in the subgroup of a single HCC exceeding 2 cm of Child-Pugh class A.
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KEY WORDS: **early hepatocellular carcinoma; hepatectomy; radiofrequency ablation**

INTRODUCTION

Hepatocelluar carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer death worldwide [1]. Although the majority of cases are still found in Asia and Africa, recent studies have shown that the incidence and mortality rates of HCC are increasing in North America and Europe [2]. Over the past two decades, great progress has been made in the diagnosis of HCC using non-invasive diagnostic modalities, and it is feasible to make early detection of HCC. Current options for the treatment of the early HCC consist of surgical resection, liver transplantation, transcatheter arterial chemoemolization (TACE), and percutaneous tumor ablation. These modalities have all been used for HCC patients according to the clinical characteristics of their tumors and the hepatic functional reserve of the patients. Hepatic resection has been shown to be the most efficacious treatment for HCC [3]; however, hepatic resection is limited to patients with good hepatic functional reserve. Radiofrequency ablation (RFA) is a recently introduced technique that is rapidly being adopted worldwide because of its greater efficacy for local cure compared with ethanol injection [4,5]. RFA is usually indicated for patients with three or fewer nodules, none of which exceed 3 cm in diameter [6]. Livraghi et al. [7] showed that RFA is just as effective as surgery for the treatment of very early HCC (single HCC nodules measuring 2.0 cm or less) in terms of sustained local disease control and survival. They advocated that RFA can be considered as the preferred treatment for patients with single HCC of 2.0 cm or less, even when surgical resection is possible. Recent, studies compared local ablation therapies with surgical resection [8–14]. However, few studies have evaluated the results of RFA in comparison with surgical resection within a subgroup (e.g., nodules $\leq$2.0 cm vs. >2.0 cm, and single vs. multiple HCCs) analysis of patients with early HCC (three or fewer nodules that are $\leq$3 cm in diameter). The aim of this retrospective study is to compare the patients with early HCC who were submitted to surgical resection and RFA from these points of view.

PATIENTS AND METHODS

From 2001 to 2007, 286 patients underwent liver resection, or RFA for single or multiple (less than 3) HCC measuring $\leq$3 cm as an initial treatment at Hiroshima University Hospital.

The diagnosis of HCC was based on routine imaging modalities including ultrasonography (US), computed tomography (CT) during hepatic angiography, and magnetic resonance imaging (MRI). HCC was diagnosed based on the following classic imaging manifestations: hyperattenuation on CT during hepatic arteriography and hypoattenuation on CT during arterial portography [15]. In case of hypovascular lesion, fine-needle biopsy was performed to obtain histological confirmation in patients who underwent RFA. Before treatment, all patients underwent liver function tests including bilirubin, albumin,

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prothrombin time, and indocyanine green retention rate at 15 min (ICGR 15) tests.

Hepatic Resection

In the current study, 199 patients were subjected to surgical resection of early HCC. The surgical procedure was determined according to the extent of the tumor, hepatic reserve function, and the patients' wishes. Liver function was assessed by Child-Pugh classification and ICGR 15. If liver function would allow, anatomic resection (segmentectomy (n = 76), sectionectomy (n = 11), or hemihepatectomy (n = 5)) was performed. In patients with insufficient hepatic reserve, limited resection (n = 107) was performed. For example, right hemihepatectomy could be tolerated if ICGR 15 was in the normal range. One-third of the liver parenchyma could be resected for patients with ICGR 15 of 10–19%, segmentectomy was possible with ICGR 15 of 20–29%, and limited resection was possible with ICGR 15 of 30% and more [16]. The procedures of hepatectomy were the same as those described previously [17,18].

RFA

Eighty-seven patients were subjected to RFA. Patients requesting not to undergo hepatectomy underwent RFA. Among the 87 patients, 69 patients were diagnosed as HCC based on CT imaging. The remaining 18 patients were diagnosed as HCC by histopathological methods. Patients were treated with RFA following TACE, if HCC nodules had hypervascularity. TACE was performed an average 3 days before RFA TACE was performed through the femoral artery using the technique of Seldinger under local anesthesia. An angiographic catheter was inserted selectively into the hepatic feeding artery of a segment or subsegments containing the target tumor. We used cisplatinum (Randa; Nippon Kayaku, Tokyo, Japan) as an anticancer drug mixed with iodized oil (Lipiodol; Nihon Schering, Tokyo, Japan) at a concentration of 10 mg/ml and injected at a dose of 10–40 mg/person. The selected dose was based on tumor size. Injection was discontinued upon full accumulation of iodized oil in the tumor vessels. No gelatin sponge or coil embolization was used after TACE in the present study.

RFA was conducted using a commercially available system (Cool-tip RF system; Radionics, Burlington, MA) and electrode that was 17-gauge. Sixty-nine patients whose tumor had hypervascularity were treated with a combination of TACE with RFA. The remaining 18 patients were treated by RFA alone. All patients underwent RFA with a percutaneous approach under real-time ultrasonographic guidance in a ward setting under local anesthesia and conscious sedation [19]. The treatment response was evaluated using CT image. When the diameter of the non-enhancing area was greater than that of the ablated nodule, RFA was considered to have produced a complete effect. HCCs with incomplete response were reevaluated for a new session.

Follow-up

Follow-up evaluation after the surgery or RFA consisted of blood chemistry tests and measurements of tumor markers including α-fetoprotein (AFP) and Des-γ-carboxy prothrombin (DCP), every month. Patients were examined by ultrasound every 3 months and by computed tomographic (CT) scan every 6 months. When recurrence was indicated by any of these examinations, patients underwent CT during arterial portography and arteriography.

Complications were stratified according to the Clavien classification of postoperative surgical complications [20] and imaging-guided tumor ablation: standardization of terminology and reporting [21]. Major complications were defined as those which required treatment or additional hospitalization, or which resulted in permanent adverse sequelae (Clavien classification grade II or higher). This includes any case in which a blood transfusion or interventional drainage procedure is required.

Treatment for Recurrence

All patients with intrahepatic recurrence were managed with ablative therapies (RFA or ethanol injection), TACE, or surgery including liver transplantation according to the same criteria used at the time of initial resection.

Histopathological Examination

The resected specimens were serially sectioned at 10-mm intervals and examined macroscopically. The criteria used to identify intrahepatic micrometastasis were essentially those proposed by the Liver Cancer Study Group of Japan; that is, tumors surrounding the main tumor with multiple other satellite nodules or small solitary tumors located near the main tumor that are histologically similar or less differentiated than the main tumor [22].

Statistical Analyses

Values for continuous variables are presented as means ± SD. Categorical variables were compared using the chi-square test and continuous variables using Student's *t*-test. Overall survival and disease-free survival analyses were carried out using the Kaplan–Meier methods; comparisons between different groups were carried out using the log rank test. The following variables were examined: age (≥70 vs. <70), sex, positivity for hepatitis C virus (HCV) antibody, ICGR 15 (≥15 vs. <15), Child-Pugh class (A vs. B), main tumor size (>20 mm vs. ≤20 mm), tumor number (single vs. multiple), plasma DCP level (≥100 AU/ml vs. <100 AU/ml), and plasma AFP level (≥100 ng/ml vs. <100 ng/ml). Multivariate analyses for survival and disease-free survival were carried out using the Cox's regression model. The regression model was used to evaluate variables found to be associated with infection by univariate analysis ($P < 0.1$). A P-value of less than 0.05 was considered significant. Calculations were performed using SPSS software (version 16; SPSS, Inc., Chicago, IL).

RESULTS

There were no differences in age and gender between the surgical resection and RFA groups. However, the hepatic resection group included more patients with hepatitis B virus (HBV) ($P = 0.049$). With regard to hepatic reserve function, ICGR 15 was significantly better in the surgical resection group than in the RFA group ($P = 0.004$); the ICGR 15 was 19.5 ± 9 in the surgical resection group and 23.7 ± 12 in the RFA group. The surgical resection group included more patients with well-preserved liver function (Child-Pugh class A) without statistical significance ($P = 0.06$). On the other hand, regarding with tumor-related factors, the tumor size and DCP level were significantly greater in the surgical resection group than in the RFA group ($P = 0.001$ and 0.03, respectively), and the tumor number was also greater in the surgical resection group than in the RFA group with statistical significance ($P = 0.023$). The mean follow-up of surgical resection and RFA groups were 35 ± 2.5 and 32 ± 2.5 months, respectively. There was no significant difference in overall survival between two groups ($P = 0.11$); the 3-year overall survival rates were 91% in the surgical resection group and 81% in the RFA group (Fig. 1). There was also no significant difference in disease-free survival between two groups ($P = 0.88$); the 3-year disease-free survival rates were 41% in the surgical resection group and 34% in the RFA group

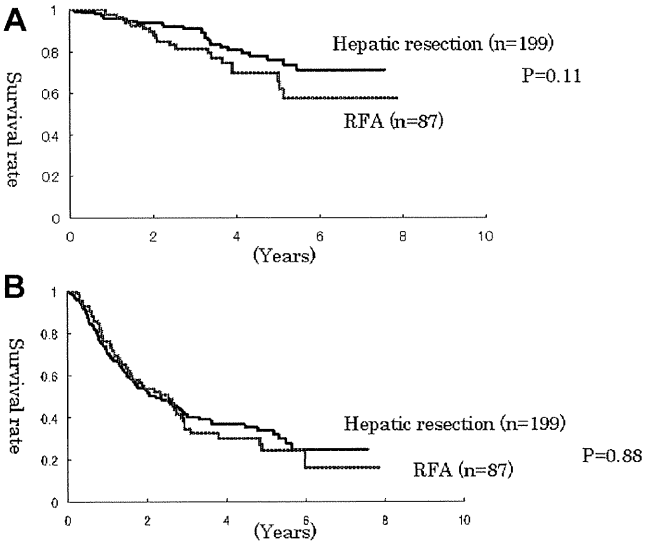

Fig. 1. **A**: Comparison of overall survival rates between patients in the surgical resection and the RFA groups. **B**: Comparison of disease-free survival rates between patients in the surgical resection and RFA groups.

(Fig. 1). Each clinical characteristic including complication was compared between the hepatic resection and RFA groups by univariate analysis, as presented in Table I. There was no mortality during initial hospital stays in both hepatic resection and RFA groups except for one patient who died as a result of suicide within 1 month of hepatic resection. There were no major complications after RFA, whereas major complications occurred in seven patients after hepatectomy. The rate of morbidity after hepatectomy tended to be higher than that after RFA ($P = 0.076$). The hospital stay of hepatectomized patients was significantly longer as compared to that of patients who had underwent RFA ($P = 0.0001$). There was recurrence at the site of the treated tumor in 4 patients who underwent RFA. Complete necrosis was confirmed by imaging in 92% of patients with RFA. Among the four patients who showed recurrence at the site of the treated tumor, three patients had HCC with tumor size exceeding 2 cm (tumor size: 2.0, 2.5, and 3.0 cm), and one patient had HCC with tumor size of 1.5 cm which was located near the liver surface.

Next, subgroup comparisons of overall and disease-free survivals were made between surgical resection and RFA groups (Table II). In subgroup analysis for a single HCC with tumor size exceeding 2 cm in Child-Pugh class A, the disease-free survival was longer in the surgical resection group (n = 72) than in the RFA group (n = 15) with statistical significance ($P = 0.048$); the 3-year disease-free survival rates were 43% in the surgical resection group and 27% in the RFA group (Fig. 2B). In the same subgroup, however, the overall survival was longer in the surgical resection group than in the RFA group without statistical significance ($P = 0.57$); the 3-year overall survival rates were 88% in the surgical resection group and 74% in the RFA group. For multiple HCCs with tumor size exceeding 2 cm in Child-Pugh class A, the overall and disease-free survival rates were longer in the surgical resection (n = 27) than RFA groups (n = 5) without statistical significance. On the other hand, in the subgroup of a single HCC with tumor size $\leq$2 cm in Child-Pugh class A, the overall and disease-free survival rates were almost the same for the surgical resection (n = 53) and RFA (n = 41) groups; the 3-year overall and disease-free survival rates were 95% and 59%, respectively, in the surgical resection group and 94% and 48%, respectively, in the RFA group (Fig. 2A). Moreover, for multiple HCCs with tumor size $\leq$2 cm in Child-Pugh class A, the overall and disease-free survival rates were also almost the same for the surgical resection (n = 30) and RFA groups (n = 11). The subgroup analyses of patients with Child-Pugh class B could not be precisely evaluated due to the small number (less than 4) of cases in each subgroup.

Table III summarizes the results of univariate analyses for all patients according to the clinical characteristics. The Child-Pugh class B ($P = 0.001$) and the tumor number ($P = 0.025$) were significant adverse prognostic factors for overall survival. Similarly, HCV positivity ($P = 0.02$), ICGR 15 $\geq$ 15% ($P = 0.043$), and the tumor number (2 or 3) ($P = 0.0002$) were significant adverse prognostic factors for disease-free survival. In multivariate analyses, Child-Pugh class B ($P = 0.043$) was an independent variable related to adverse overall survival (Table IV). The overall survival rates at 1, 3, and 5 years of 254 patients of Child-Pugh class A were 97%, 91%, and 77%, respectively. The corresponding survival rates of 32 patients of Child-Pugh class B were 94%, 67%, and 56%, respectively.

Table V presents the pathological findings. The incidence of regional cancer spread was significantly lower for HCCs smaller than

TABLE I. Background Characteristics of Patients With Resection or RFA

Variables	Hepatic resection (n = 199)	RFA (n = 87)	*P*-value
Gender (male/female)	137 (68%)/62 (31%)	53 (61%)/34 (39%)	0.19
Age (year)	65.7 ± 9.0	66.3 ± 8.2	0.6
Virus (B/C/others)	38 (19%)/145 (73%)/16 (8%)	9 (10%)/73 (84%)/5 (5%)	0.049
Total bilirubin (mg/dl)	0.86 ± 0.34	0.93 ± 0.36	0.1
Prothrombin time (%)	86.6 ± 14.9	83.7 ± 15.4	0.139
Serum albumin (g/dl)	3.82 ± 0.47	3.78 ± 0.50	0.537
Platelet count (10^4/mm^3)	11.8 ± 7.1	10.5 ± 8.6	0.21
ICG R 15 (%)	19.5 ± 9.0	23.7 ± 12	0.004
Child-Pugh classification (A/B)	182 (91%)/17 (9%)	72 (83%)/15 (17%)	0.06
Tumor size (mm)	2.1 ± 0.63	1.8 ± 0.52	0.001
Tumor number (single/multiple)	132 (66%)/67 (34%)	67 (77%)/20 (23%)	0.023
DCP (AU/ml)	197 ± 756	72 ± 223	0.03
AFP (ng/ml)	310 ± 1322	85 ± 166	0.11
Hospital stay (day)	15 ± 8	8 ± 3	0.0001
Major complications			0.076
Ascites or pleural effusion	2 (1%)	0	
Rupture of esophageal varices	2 (1%)	0	
Biliary leakage	3 (2%)	0	

RFA, radiofrequency ablation; B, hepatitis B virus; C, hepatitis C virus; ICGR 15, indocyanine green retention rate at 15 min; DCP, Des-γ-carboxy prothrombin; AFP, alpha-fetoprotein.

TABLE II. Overall Survival and Disease-Free Survival Rate for Patients of Child-Pugh Class A

	Overall survival rate (%)				Disease-free survival rate (%)			
Factor	1 year	3 years	5 years	*P*-value	1 year	3 years	5 years	*P*-value
Single HCC >2 cm				0.57				0.048
Resection (n = 72)	94	88	83		71	43	36	
RFA (n = 15)	100	74	74		44	27	9	
Multiple HCC >2 cm				0.18				0.98
Resection (n = 27)	96	96	43		60	28	22	
RFA (n = 5)	100	75	38		80	0	0	
Single HCC ≤2 cm				0.46				0.58
Resection (n = 53)	100	95	88		90	59	53	
RFA (n = 41)	97	94	83		81	48	43	
Multiple HCC ≤2 cm				0.98				0.98
Resection (n = 30)	92	92	69		61	22	22	
RFA (n = 11)	100	92	73		80	18	18	

RFA, radiofrequency ablation.

2 cm than for HCC >2 cm; with microvascular invasion (22% vs. 4.3%) and micrometastasis (20.3% vs. 8.3%) being more common in HCCs >2 cm compared to those ≤2 cm.

Ninety-seven (49%) of the patients in the hepatic resection group and 43 (49%) of the patients in the RFA group showed HCC recurrences. The pattern of recurrence and the details of treatments for the recurrences in both groups are shown in Table VI. The main treatment for recurrence was TACE (34%), followed by RFA (28%) and repeat hepatectomy (23%) in the surgical resection group, whereas the main treatment for recurrence was RFA (37%), and followed by TACE (35%) and hepatectomy (16%) in the RFA group. One patient underwent salvage liver transplantation for recurrence in the surgical resection group. The proportion of patients with extrahepatic recurrence tended to be higher in the hepatic resection group ($P = 0.07$), but the modalities of the treatments used for recurrence did not differ among the two groups.

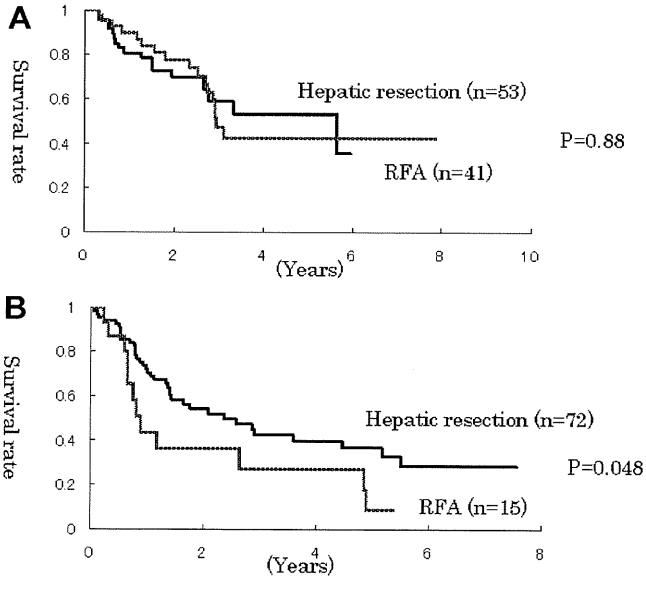

Fig. 2. **A**: Comparison of disease-free survival rates in patients with a single HCC with tumor size less than 2 cm in Child-Pugh A between patients in the surgical resection and RFA groups. **B**: Comparison of disease-free survival rates in patients with a single HCC with tumor size >2 cm in Child-Pugh A between patients in the surgical resection and RFA groups.

DISCUSSION

Livraghi et al. [7] recently demonstrated that the estimated 3- and 5-year survival rates for the potentially operable subgroup (100 patients with a single HCC ≤2 cm) were 89% and 68%, respectively. They showed that the 5-year survival rate in their study was comparable to that reported by the Liver Cancer Study Group of Japan, which revealed a 5-year survival rate of 70% for 2078 patients. They concluded that RFA can be considered the preferred treatment for patients with single HCC ≤2 cm, even when surgical resection is possible, since RFA is much less invasive and has a lower complication rate, and other approaches can be used as salvage therapy for the few cases in which RFA is unsuccessful or unfeasible. In our study, a combination of TACE and RFA was performed in the majority of patients with hypervascular HCC nodules who did not undergo surgical resection. The diagnosis by CT imaging has the possibility of misdiagnosis of HCC for nodule measuring 2.0 cm or less. Vascular occlusion by TACE permits the formation of larger thermal lesions by reducing heat loss [23,24]. In addition, the accumulation of lipiodol might be useful for obtaining the border of the tumors at CT scan after RFA [19]. In our current study, RFA for HCC smaller than 2 cm has overall and disease-free survival rates similar to those for the resection group. The previous histopathologic studies have shown that, although HCC nodules measuring 1.5 cm or less are uniformly well differentiated, those between 1.5 and 2.0 cm in diameter often contain zones of less differentiated tissue with more intense proliferative activity [25]. Takayama et al. [26] also found that among 70 patients with an early single HCC of 2 cm or less in diameter, only 15 HCC lesions were well-differentiated, and microscopic regional spread (vascular invasion and micrometastasis) was identified in 23 (33%) patients. On the other hand, Wakai et al. [27] shown that vascular invasion was more frequent in patients with HCC >2 cm (16/62, 26%) than in patients with HCC ≤2 cm (1/23, 4%, $P = 0.033$). In the current study, the incidence of micrometastasis and microvascular invasion was significantly lower among patients with HCCs 2 cm or less in diameter than among patients with HCCs larger than 2.0 cm in diameter. Recently, Shi et al. [28] found that among patients with HCCs ≤3 cm, 38 (86%) out of 44 identified micrometastases were located within 1 cm of tumor in the same direction of portal venous, and a resection margin of 1.0 cm is recommended for HCCs ≤3 cm. Theoretically, a single electrode insertion can produce a necrotic area of up to 3.0 cm in diameter, thus allowing full ablation of a 2-cm tumor plus a 0.5–1.0 cm safety margin. Our studies have suggested that the choice of RFA does not matter for patients with single or multiple (less than 3) HCC ≤2 cm, if HCC lesions cannot be visualized by US or are close to anatomic structures that might be damaged by RFA.

TABLE III. Univariate Analysis of Clinical Factors for Overall Survival and Disease-Free Survival Rate

	Overall survival rate (%)				Disease-free survival rate (%)			
Factor	1 year	3 years	5 years	*P*-value	1 year	3 years	5 years	*P*-value
Age (year)				0.53				0.7
≤70 (n = 175)	97.6	89.1	76.1		73.1	38.4	31.7	
>70 (n = 111)	94.1	85.5	71.1		72.9	39.4	27.5	
Gender				0.15				0.8
Male (n = 190)	96.6	86.4	72.2		72.4	40.4	34.4	
Female (n = 96)	95.6	89.9	77.3		74.4	35.2	20.2	
Virus				0.09				0.02
HCV (n = 218)	96	86.3	70.9		71.8	31.9	34.4	
Non-HCV (n = 68)	96.8	89.9	84.6		74.4	54	47.6	
Child-Pugh classification				0.001				0.227
A (n = 254)	96.6	90.7	76.6		72.5	39.2	32.6	
B (n = 32)	93.5	67	56.2		74.3	34.3	10.7	
ICGR 15 (%)				0.6				0.043
<15 (n = 148)	96.6	85.1	79		75.1	46.9	36.9	
≥15 (n = 137)	95.6	90.4	68.9		70.2	28.6	22.6	
Tumor size (mm)				0.26				0.07
≤2.0 (n = 157)	96.4	89.8	78.7		79.2	40.2	33.3	
>2.0 (n = 129)	96	85.6	69.8		65.1	36.2	27	
Tumor number				0.025				0.0002
Single (n = 199)	96.8	87.2	80.4		75.9	45.3	36.7	
2 or 3 (n = 87)	95	88.9	59.6		65.1	23.9	16.6	
DCP (AU/ml)				0.11				0.46
<100 (n = 227)	97.1	89.5	76.1		73.1	38.7	30.5	
≥100 (n = 59)	92.8	85.6	69.3		71.2	39.3	30.6	
AFP (ng/ml)				0.65				0.64
<100 (n = 215)	96.5	90.2	74.8		73	38.1	30	
≥100 (n = 71)	95.5	89.4	74.9		73.2	42.1	33.8	
Treatment				0.11				0.88
Resection (n = 199)	95.6	90.9	76		71.4	41.2	33.7	
RFA (n = 87)	97.6	81.4	71		76.5	34.3	24.7	

HCV, hepatitis C virus; ICGR 15, indocyanine green retention rate at 15 min; DCP, Des-γ-carboxy prothrombin; AFP, alpha-fetoprotein.

A preliminary report of the Japanese nationwide survey has shown that surgical resection provides a lower time-to-recurrence rate than RFA does among patients with HCCs no more than three tumors (≤3 cm) [12]. In the current study, we have also shown that in subgroup analysis of a single HCC with tumor size >2 cm in Child-Pugh class A, the disease-free survival was longer in the surgical resection group than in the RFA group with significance. The overall survival was longer in the surgical resection group than in the RFA group, although the result was not significant. Our histopathological study has shown that the incidence of micrometastasis was significantly higher among patients with HCCs exceeding 2 cm in diameter (20%) than among patients with HCCs 2.0 cm or less in diameter (8.3%). These findings have suggested that RFA is less effective than hepatic resection to eradicate venous tumor thrombi and micrometastasis in the adjacent liver in addition to the complete removal of the primary HCC with tumor size >2 cm [29,30]. Surgical resection may provide better long-term disease-free survival than RFA in the subgroup of a single HCC exceeding 2 cm of Child-Pugh class A.

We have shown that in subgroup analysis of multiple HCCs exceeding 2 cm in Child-Pugh class A, the overall survival and the disease-free survival in the surgical resection group was not significant different from that in the RFA group. The strategy for multiple HCCs larger than 2 cm in Child-Pugh class A remains unclear because of small sample number in RFA group.

TABLE IV. Multivariate Analysis of Overall Survival

Variable	HR	95% CI	*P*-value
Child-Pugh class (B vs. A)	1.669	1.016–2.741	0.043

In our study, Child-Pugh class A and a single tumor were significant favorable prognostic factors for overall survival, and HCV negativity, lower ICGR 15, and a single tumor were significant favorable prognostic factors for disease-free survival in univariate analysis, although in a multivariate study only Child-Pugh class A was an independent favorable factor for overall survival. The preliminary report of the Japanese nationwide survey has shown that in multivariate analysis, low tumor marker, tumor size <2 cm, better liver function (Child-Pugh class A), and the presence of HCV infection were favorable factors for overall survival, and a single tumor, low tumor marker levels, small tumor size, the absence of HCV, and younger age were negative factors for recurrence [12]. These results are similar to trends found in the nationwide study.

Radiofrequency is much less invasive, involves a short hospital stay, and has low mortality associated with the procedure. With the intention of avoiding the risk of hepatic failure that can follow hepatic resection, percutaenous ablation treatments have been proposed due to the efficacy, tolerability, and low risk of the procedure. However, in the

TABLE V. Pathological Characteristics of HCC of Patients With Hepatic Resection

Characteristics	HCC >2 cm (n = 103)	HCC ≤2 cm (n = 96)	*P*-value
Histological type			
Well/moderate/poor/unknown	11/75/11/6	22/65/4/5	0.023
Regional cancer spread			
Microvascular invasion	23 (22%)	4 (4.3%)	0.0001
Intrahepatic micrometastasis	21 (20.3%)	8 (8.3%)	0.027

TABLE VI. Recurrence and Treatments for Recurrence After Hepatic Resection or RFA

	Hepatic resection (n = 199)	RFA (n = 87)	*P*-value
HCC recurrence: yes[a]	97 (49%)	43 (49%)	0.84
Pattern of recurrence[b]			0.07
Intrahepatic	86 (89%)	43 (100%)	
Intahepatic + extrahepatic	7 (7%)	0 (0%)	
Extrahepatic	4 (4%)	0 (0%)	
Treatment: yes[b]	93 (96%)	41 (95%)	0.5
Main modalities[b]			0.67
Hepatectomy	23 (24%)	7 (16%)	
RFA	27 (28%)	16 (37%)	
PEI	3 (3%)	2 (5%)	
TACE	33 (34%)	15 (35%)	
Liver transplantation	1 (1%)	0 (0%)	
Others	6 (6%)	1 (2%)	

RFA, radiofrequency ablation; PEI, percutaneous ethanol injection; TACE, transcatheter arterial chemoembolization

[a]Data are expressed as the number of patients (percentage of total patients).

[b]Data are expressed as the number of patients (percentage of patients who had a recurrence).

current study, hepatic resection has been considered as an acceptable treatment, because the procedure-related mortality was zero after hepatectomy, and there was no significant difference in the incidence of morbidity between the two groups, regardless of the high tendency of the incidence of morbidity after hepatic resection.

Our retrospective study had some drawbacks. Clinical characteristics that can strongly influence outcomes differed significantly between the surgical resection group and the RFA group, as shown in other studies. In the current study, the proportion of the multinodular HCC patients and the levels of DCP were higher in the resection group than those in the RFA group, whereas the proportion of poor function liver reserve was lower in the resection group than that in the RFA group. Because multiple nodules and poor function liver reserve are major risks of recurrence, we conducted subgroup analysis according to the tumor size, tumor number, and Child-Pugh class. Ultimately, a randomized controlled trial would be necessary to prospectively determine if RFA and surgery are comparable therapies for early stage HCC.

In conclusion, RFA can be considered the preferred treatment for patients with single or multiple HCC $\leq$2 cm of Child-Pugh class A. Our results suggest that surgical resection may provide better long-term disease-free survival than RFA does in the subgroup of a single HCC exceeding 2 cm of Child-Pugh class A. A large prospective trial comparing surgical resection with RFA is on-going in the Japanese nationwide study, and thus, clear-cut guidelines are expected to be established in the near future.

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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Clinical features and prognosis in patients with hepatocellular carcinoma that developed after hepatitis C virus eradication with interferon therapy

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Abstract
Background We evaluated the clinical features and the prognostic factors of hepatocellular carcinoma (HCC) developed after hepatitis C virus (HCV) eradication with interferon (IFN) therapy.
Methods Forty-one consecutive patients who developed HCC after HCV eradication with IFN therapy were enrolled. Clinical features were reviewed, and overall survival and associated factors were analyzed. The recurrence rate in 26 patients receiving radical therapy was also analyzed.
Results Twenty patients developed HCC within 5 years after the end of IFN therapy, 9 patients developed the disease from 5 to 10 years after the end of the therapy, 9 patients developed the disease from 10 to 15 years after the end of the therapy, and 3 patients developed the disease from 15 years after the end of the therapy. Multivariate analysis of independent variables for the development of HCC within 5 years identified age >55 years at HCV eradication ($P = 0.007$) and heavy alcohol intake ($P = 0.009$). The 5-year survival rate was 64%. On multivariate analysis of overall survival for the 41 patients, the only risk factor with prognostic influence was radical therapy ($P = 0.010$), which was associated with a cumulative 5-year survival rate of 91%. The only independent factor for the receipt of radical therapy was regular surveillance for HCC ($P = 0.004$). Among patients receiving radical therapy, the 3- and 5-year recurrence rates were 18 and 18%, respectively.
Conclusion We found that, despite HCV eradication, patients with the risk factors of high age at HCV eradication and heavy alcohol intake might be at heightened risk for the development of HCC within 5 years after HCV eradication. In contrast, risk factors for the development of HCC more than 10 years after HCV eradication were uncertain. These findings indicate the need for long-term surveillance for HCC after HCV eradication.

Keywords Hepatocellular carcinoma · Hepatitis C virus · Interferon · Sustained virological response · Surveillance

Introduction

Hepatitis C virus (HCV) infection is a common cause of chronic hepatitis and hepatocarcinogenesis worldwide [1–3]. Hepatocellular carcinoma (HCC) is at present the fifth most common cancer in the world, responsible for 500,000 deaths globally every year [4], and its incidence is increasing due to hepatitis B and C virus infection. In Japan, approximately 80% of patients with HCC have HCV infection. Particularly among cirrhotic patients with antibodies to HCV, the HCC occurrence rate is increasing steadily, with a yearly reported incidence of 1.4–7% [5–7]. While recent advances in imaging and treatment have improved the prognosis of patients with HCV-related HCC, outcomes remain unsatisfactory, highlighting the need to improve not only the diagnosis and treatment of HCC, but also its prevention. However, few studies have evaluated the effect of eradicating HCV on the prevention of HCC.

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Interferon (IFN), first used in 1986 [8], is the only approved antiviral agent able to eradicate the virus. Given the many reports of the efficacy of IFN-based therapy in ameliorating hepatic inflammation, fibrosis, and serum alanine aminotransferase levels and in decreasing circulating HCV-RNA levels and the risk of HCC [9–14], we speculated that IFN treatment and HCV eradication would be an effective cancer chemoprevention strategy for patients with chronic hepatitis C. Supporting this, one study estimated 7-year cumulative incidence rates of HCC in sustained responders, transient responders, and non-responders of 4.3, 4.7, and 26.1%, respectively [9], while several others have reported that the decrease in incidence of HCC with IFN treatment is particularly clear among patients with a sustained virological response (SVR) [10, 11, 15–17]. In contrast, however, others have reported the development of HCC in patients with SVR [18–24]. These conflicting findings indicate that the risk factors of and optimum surveillance for HCC after HCV eradication have not been fully elucidated. Moreover, while both the diagnosis and treatment of HCC have shown substantial progress, prognosis and recurrence after radical treatment for HCC in patients with HCV eradication also remain unclear.

In particular, only one study has described the development of HCC from 10 years after HCV eradication [25], and little is known about the length of time between HCV eradication and HCC occurrence, the prognosis of HCV-associated HCC, the overall survival rate after radical treatment for HCC, and the recurrence rate after hepatic resection or ablative therapy.

Here, we identified risk factors for the development of HCC within 5 years after HCV eradication. We also analyzed the prognosis and rate of recurrence of HCC after radical treatment in patients who had previously undergone HCV eradication.

Patients and methods

Patients

We retrospectively reviewed 41 consecutive cases of HCC which developed after the eradication of HCV with IFN therapy from February 1995 to December 2009 at Hiroshima University Hospital. All patients were hepatitis B surface antigen-negative.

The clinical characteristics of the 41 patients are shown in Table 1. The patients consisted of 35 males and 6 women. The median age of all patients was 67 years (range, 54–87 years) at initial HCC development and 60 years (range, 42–78 years) at HCV eradication at the time of the study. Thirteen patients had diabetes mellitus, 18 had hypertension, 23 had heavy alcohol consumption of more than 80 g/day for 5 years after HCV eradication, and 16 had a body mass index (BMI) >25 kg/m^2. At the initial diagnosis of HCC, median laboratory values were as follows: alanine aminotransferase, 19 IU/l (range 8–345 IU/l); aspartate aminotransferase, 26 IU/l (range 12–215 IU/l); serum albumin, 4.4 mg/dl (range 3.2–5 mg/dl); platelet count, 14.9 $\times$ 10^4/μl (range 4.5–88.8 $\times$ 10^4/μl); α-feto-protein (AFP), 8 ng/ml (range 5–371,000 ng/ml): and protein induced by vitamin K absence or antagonist II (PIVKA-II), 146 mAU/ml (range 7.7–686,090 mAU/ml). Among the 19 patients who were examined for serum iron and ferritin, the median laboratory values were 84 μg/dl (range 28–268 μg/dl) and 143.3 ng/ml (range 13–996 ng/ml), respectively. Among the 33 patients who received liver biopsies before IFN therapy, 3 were categorized as showing histological fibrosis stage F1, 17 were categorized as F2, 7 as F3, and 6 as F4.

On TNM staging for HCC according to the criteria of the Liver Cancer Study Group of Japan, 13 patients were categorized as stage I, 10 as stage II, 8 as stage III, and 10 as stage IVa, with none categorized as stage Vb. The underlying liver damage in all patients was chronic hepatitis or Child–Pugh class A cirrhosis. Median duration from the end of IFN therapy to the initial diagnosis of HCC was 55 months (range 4–184 months). Nineteen of the patients had received regular surveillance for HCC by ultrasonography, dynamic computed tomography (CT), or the analysis of serum HCC-specific tumor markers (AFP, PIVKA-II) at least annually after HCV eradication. Of the other 22 patients who had not received regular surveillance for HCC, HCC was detected in 9 through medical health checks, in 6 through the development of abdominal pain, and in 7 through treatment of other diseases.

Diagnosis of HCC

Diagnosis of HCC was based on the hypervascular staining pattern of the arterial phase and the hypovascular staining pattern of the portal phase, and confirmed by dynamic computed tomography (CT), magnetic resonance imaging, or angiography. Tumors without enhancement upon imaging were diagnosed by fine-needle biopsy.

Treatment procedures

Of the 26 patients [median age 68 years (range 55–81 years), 21 men] who underwent radical treatment, 17 received liver resection and 9 received radiofrequency ablation (RFA). Radical treatment was not performed in the other 15 patients due to advanced HCC stage.

Of these 15 patients, 2 received palliative hepatic resection; 5 received transcatheter arterial chemoembolization (TACE); 5 received hepatic arterial infusion of

Table 1 Clinical characteristics of patients developing HCC following HCV eradication with IFN therapy

Total	41
Age[a] (years, range)	67 (54–87)
Sex (male/female)	35/6
Diabetes mellitus (with/without)	13/28
Hypertension (with/without)	18/23
Alcohol intake (with/without)	23/18
Age at HCV eradication[a] (years, range)	60 (42–78)
Serum AST[a] (IU/l, range)	26 (12–215)
Serum ALT[a] (IU/l, range)	19 (8–345)
Albumin[a] (g/dl, range)	4.4 (3.2–5)
Platelet count[a] ($\times 10^4$/μl, range)	14.9 (4.5–88.8)
Hemoglobin A1c[a] (%, range)	5.4 (4.5–8.7)
Serum iron[a] (μg/dl, range)	84 (28–268)
Ferritin[a] (ng/ml, range)	143.3 (13.4–996)
Body mass index (kg/m^2, ≥25/<25)	16/25
Histological activity score[b] (A1/A2/A3/NA)	12/19/2/8
Histological fibrosis stage[b] (F1/F2/F3/F4/NA)	3/17/7/6/8
HCC stage[c] (I/II/III/IVa/IVb)	13/10/8/10/0
Maximum tumor size (mm, ≤20/>20)	17/24
No. of HCC tumors (single/multiple)	21/20
AFP[a] (ng/ml, range)	8 (5–371,000)
PIVKA-II[a] (mAU/ml, range)	146 (7.7–686,090)
Regular surveillance (with/without)	19/22
Radical treatment (with/without)	26/15
Development of HCC[d] (<5/≥5 years)	20/21

Alcohol intake, ≥80 g/day for more than 5 years; regular surveillance, defined as ultrasonography, dynamic computed tomography (CT), or analysis of serum hepatocellular carcinoma (HCC)-specific tumor markers (AFP, PIVKA-II) at least annually after interferon (IFN) therapy; radical treatment, liver resection or radiofrequency ablation

HCV hepatitis C virus, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *NA* not available, *AFP* alpha-fetoprotein, *PIVKA-II* protein induced by vitamin K absence or antagonist

[a] Median

[b] Histological finding before IFN therapy

[c] Determined according to the criteria set by the Liver Cancer Study Group of Japan

[d] Development of HCC within or more than 5 years after the eradication of HCV

chemotherapy, due to portal vein tumor thrombosis and the impossibility of receiving TACE; and 3 received best supportive care.

Follow-up after treatment for initial HCC

After treatment for the initial HCC, all patients underwent liver function tests; bimonthly analysis of serum tumor markers (AFP, lectin fraction 3, PIVKA-II); trimonthly abdominal ultrasonography; and biannual dynamic CT. Suspected recurrence was investigated by additional examinations, including CT during arteriography or tumor biopsy.

Statistical analysis

Continuous variables were expressed as means ± standard deviation and compared using the Mann–Whitney *U*-test. Categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Overall survival and recurrence rates were calculated by the Kaplan–Meier method, and differences between groups were compared using the log-rank test. Clinical record variables that were of potential prognostic value were dichotomized and analyzed for their effect on overall survival. Multivariate analysis was conducted with a Cox proportional hazard model using the stepwise selection of variables or two logistic analyses. All statistical analyses were performed using the SPSS software package (version 12.0 for Windows; SPSS, Chicago, IL, USA), with $P < 0.05$ denoting statistical significance.

Results

Risk factors for the development of HCC within 5 years after HCV eradication

Twenty patients developed HCC within 5 years after completing IFN therapy, 9 patients developed HCC from 5 to 10 years after completing the IFN therapy, 9 patients developed HCC from 10 to 15 years after completing the IFN therapy, and 3 patients developed HCC more than 15 years after completing the IFN therapy. Because the median time period from the end of IFN therapy to initial HCC diagnosis was 4.5 years, we compared background characteristics between patients who developed HCC within and more than 5 years after HCV eradication.

Univariate analysis identified advanced age (≥55 years) at HCV eradication and heavy alcohol intake (≥80 g/day for more than 5 years) as significant risk factors associated with the development of HCC within 5 years after completing IFN therapy (Table 2).

Multivariate analysis of the predictive value of each variable for the development of HCC within 5 years also identified advanced age (>55 years) at HCV eradication (risk ratio [RR] 26.615; 95% confidence interval [CI] 2.409–294.165; $P = 0.007$) and heavy alcohol intake (≥80 g/day for more than 5 years; RR 8.898; 95% CI 1.744–45.386; $P = 0.009$) (Table 3). Liver biopsies were not available for eight patients who had been referred from other hospitals. Excluding these, five of six patients who had a histological fibrosis stage of F4 developed HCC

Table 2 Univariate analysis of risk factors associated with the development of HCC within 5 years after HCV eradication with IFN therapy

Variable	<5 years ($n = 20$)	≥5 years ($n = 21$)	P value
Sex (male/female)	19/1	17/4	0.343
Age at HCV eradication (years, ≥55/<55)	19/1	12/9	0.009
Serum AST (IU/l, ≥25/<25)	8/12	10/11	0.756
Serum ALT (IU/l, ≥20/<20)	11/9	10/11	0.758
Albumin (g/dl, <4.3/≥4.3)	6/14	9/12	0.520
Platelet count ($\times 10^4$/μl, <15/≥15)	11/9	9/12	0.538
Body mass index (kg/m^2, ≥25/<25)	11/9	5/16	0.058
Alcohol intake (with/without)	15/5	8/13	0.028
Diabetes mellitus (with/without)	6/14	7/14	1.000
Hypertension (with/without)	8/12	10/11	0.756
Hyperlipidemia (with/without)	2/18	5/16	0.410
Serum iron (μg/dl, ≥85/<85)	12/7	6/4	NA
Ferritin (ng/ml, ≥145/<145)	11/8	6/4	NA
Histological activity score[a] (A1/A2 vs. A3)	17/1	15/0	NA
Histological fibrosis stage[a] (F1/F2/F3 vs. F4)	13/5	14/1	NA

Categorical variables were compared by using the χ^2 test or Fisher's exact test, as appropriate

Alcohol intake, ≥80 g/day for more than 5 years

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *NA* not available

[a] Histological finding before IFN therapy

Table 3 Multivariate analysis of risk factors associated with the development of HCC within 5 years after HCV eradication with IFN therapy

Variable	Risk ratio (95% confidence interval)	P value
Age >55 years at HCV eradication	26.615 (2.409–294.165)	0.007
Alcohol intake	8.898 (1.744–45.386)	0.009

Alcohol intake, ≥80 g/day for more than 5 years

within 5 years after HCV eradication. Additionally, among the 19 patients for whom the levels were measured, serum iron and ferritin levels were not associated with HCC development. In contrast with the findings within 5 years after HCV eradication, no risk factors for carcinogenesis were identified 10 years after IFN therapy.

Clinical characteristics of 12 patients who developed HCC more than 10 years after HCV eradication with IFN therapy

The clinical characteristics of the 12 patients who developed HCC more than 10 years after HCV eradication with IFN therapy are shown in Table 4. Median age at HCV eradication was 56 years (range 42–72 years). Six of these patients had diabetes mellitus, six had hypertension, five had heavy alcohol consumption of more than 80 g/day for 5 years after HCV eradication, and four had a BMI >25 kg/m^2. At the development of the initial HCC, median laboratory values were: alanine aminotransferase, 34 IU/l (range 19–92 IU/l); aspartate aminotransferase, 27.5 IU/l (range 12–80 IU/l); serum albumin, 4.4 mg/dl (range 3.7–4.7 mg/dl); and platelet count, 17×10^4/μl (range $4.5–25.2 \times 10^4$/μl). Ten of the 12 patients who developed HCC more than 10 years after HCV eradication with IFN therapy were examined for serum iron and ferritin, and had median laboratory values of 57 μg/dl (range 30–183 μg/dl) and 108.1 ng/ml (range 24.9–996 ng/ml), respectively. Eight of the 12 patients had undergone liver biopsies before IFN therapy, of whom 1 was categorized as having histological fibrosis stage F1, 3 as F2, 3 as F3, and 1 as F4.

Overall survival after diagnosis of initial HCC

The median observation period after the diagnosis of the initial HCC was 19 months (range 1–89 months). The cumulative 5-year survival rate was 64% (Fig. 1). Five patients died due to HCC and three died of other causes; namely, one due to traffic accident, one due to septic shock, and one due to neuropathy.

Table 4 Clinical characteristics of patients who developed HCC more than 10 years after HCV eradication with IFN therapy

Total	12
Age[a] (years, range)	68 (54–87)
Sex (male/female)	10/2
Diabetes mellitus (with/without)	6/6
Hypertension (with/without)	6/6
Alcohol intake (with/without)	5/7
Age at HCV eradication[a] (years, range)	56 (42–72)
Serum AST[a] (IU/l, range)	34 (19–92)
Serum ALT[a] (IU/l, range)	27.5 (12–80)
Albumin[a] (g/dl, range)	4.4 (3.7–4.7)
Platelet count[a] ($\times 10^4/\mu l$, range)	17 (4.5–25.2)
Hemoglobin A1c[a] (%, range)	5.9 (4.7–8.7)
Serum iron[a] (μg/dl, range)	57 (30–183)
Ferritin[a] (ng/ml, range)	108.1 (24.9–996)
Body mass index (kg/m^2, ≥25/<25)	4/8
Histological activity score[b] (A1/A2/A3/NA)	2/6/0/4
Histological fibrosis stage[b] (F1/F2/F3/F4/NA)	1/3/3/1/4
HCC stage[c] (I/II/III/IVa/IVb)	3/1/4/2/2
Maximum tumor size (mm, ≤20/>20)	4/8
No. of HCC tumors (single/multiple)	5/7
AFP[a] (ng/ml, range)	80.7 (5–198,500)
PIVKA-II[a] (mAU/ml, range)	483.5 (20–40,616)

Alcohol intake, ≥80 g/day for more than 5 years

AST aspartate aminotransferase, *ALT* alanine aminotransferase, *NA* not available, *AFP* alpha-fetoprotein, *PIVKA-II* protein induced by vitamin K absence or antagonist

[a] Median

[b] Histological finding before IFN therapy

[c] Determined according to the criteria set by the Liver Cancer Study Group of Japan

Prognostic factors associated with the overall survival of the 41 patients with initial HCC were further analyzed. Univariate analysis identified seven factors which had a significant positive prognostic influence on overall survival: radical treatment, age <55 years at HCV eradication, PIVKA-II ≤100 mAU/ml, AFP ≤20 ng/ml, maximum tumor size ≤20 mm, and regular surveillance for HCC (Table 5).

Multivariate analysis identified radical treatment as an independent predictor of overall survival (risk ratio 15.906; 95% CI 1.946–129.982, $P = 0.010$). Among the 26 patients who received radical treatment, the median observation period after treatment for primary HCC was 28 months (range 1–95 months). The overall survival rate in patients who received radical treatment was significantly higher than that in the patients who did not receive radical treatment, and the cumulative 5-year survival rates with and without radical treatment were 91 and 25%, respectively

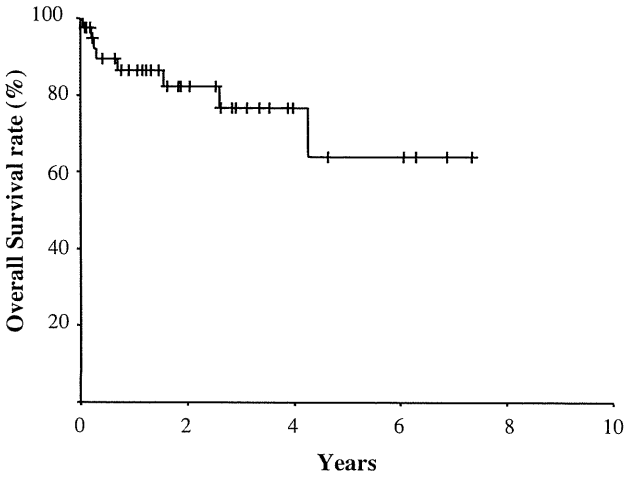

Fig. 1 The overall survival rate of patients who developed hepatocellular carcinoma (HCC) after hepatitis C virus (HCV) eradication with interferon (IFN) therapy

($P = 0.0005$) (Fig. 2). Of the 26 patients who received radical treatment, one died of neuropathy.

Comparison between characteristics of patients with and without radical treatment

Univariate analysis showed that radical treatment was significantly associated with regular surveillance for HCC, single tumor, AFP ≤20 ng/ml, and PIVKA-II ≤100 mAU/ml (Table 6). Multivariate logistic regression analysis showed that radical treatment was significantly associated with regular surveillance (risk ratio 12.278; 95% CI 2.257–66.793, $P = 0.004$).

Clinical characteristics of four patients with recurrent HCC after radical treatment

Four (15%) of the 26 patients who received radical treatment for initial HCC developed tumor recurrence, with 3- and 5-year recurrence rates both being 18% (Fig. 3). The clinical characteristics of these four patients are given in Table 7. Three of these patients were men; the median ages of all four patients were 58 years (range 54–78 years) and 61 years (range 58–80 years) at HCV eradication and initial HCC development, respectively. The median time period from the end of IFN therapy to initial HCC development was 32 months (range 10–91 months). All patients underwent hepatic resection for the initial HCC. Three patients were aged over 55 years at HCV eradication, and three had a BMI >25 kg/m^2.

In all four patients, the initial HCC showed neither microvascular invasion nor microsatellite lesions in pathological findings. The median period from the initial radical treatment to the development of recurrent HCC was

Table 5 Univariate analysis of risk factors associated with prognostic influence on overall survival for 41 patients

Variable	*P* value
Sex	
Male versus female	0.2410
Age at HCV eradication (years)	
≥55 versus <55	0.0125
Platelet count ($\times 10^4/\mu l$)	
≥15 versus <15	0.8149
Body mass index (kg/m^2)	
≥25 versus <25	0.1153
Alcohol	
Intake versus non-intake	0.9734
Development of HCC[a]	
<5 versus ≥5 years	0.4200
Maximum tumor size (mm)	
≤20 versus >20	0.0192
No. of HCC tumors	
Single versus multiple	0.1457
AFP (ng/ml)	
≤20 versus >20	0.0173
PIVKA-II (mAU/ml)	
≤100 versus >100	0.0149
Regular surveillance	
Received versus not received	0.0455
Radical treatment	
Received versus not received	0.0005

Alcohol intake, ≥80 g/day for more than 5 years; regular surveillance, defined as ultrasonography, dynamic CT, or analysis of serum HCC-specific tumor markers (AFP, PIVKA-II) at least annually after IFN therapy; radical treatment, liver resection or radiofrequency ablation

AFP alpha-fetoprotein, *PIVKA-II* protein induced by vitamin K absence or antagonist

[a] Development of HCC within or more than 5 years after the eradication of HCV

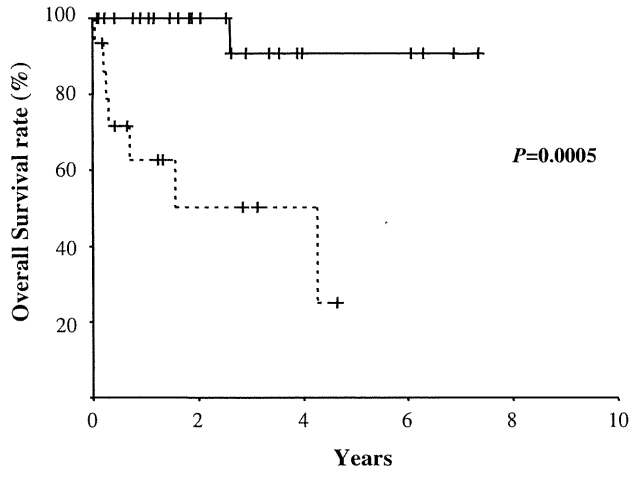

Fig. 2 Comparison of the survival rates between patients receiving radical treatment and those receiving non-radical treatment. *Solid line* patients receiving radical treatment; *dotted line* patients receiving non-radical treatment

26 months (range 12–85 years). All the recurrent tumors were single, <2 cm in diameter, and in a segment different to that of the initial HCC. Three of the four patients underwent hepatic resection and one underwent radiation therapy with TACE, with curative intent in all four patients. Case 2 developed recurrent HCC in the liver twice after primary hepatic resection, at 17 and 45 months. With regard to the pathological findings of the background liver tissues, all three patients who were examined at hepatic resection for recurrence of HCC were classified as having a fibrosis score of F2, and experienced attenuation of fibrosis.

With the exception of case 4, the patients developed the initial HCC within 5 years after HCV eradication and the recurrent HCC within slightly <2 years after hepatic resection for the initial HCC. In contrast, case 4 had longer periods between HCV eradication, initial HCC development, and HCC recurrence.

Discussion

In this study, we analyzed clinical features and prognostic factors in 41 consecutive patients who developed HCC after HCV eradication. Of these, 20 patients (49%) developed HCC within 5 years after HCV eradication, 9 (22%) developed HCC after 5–10 years, 9 (22%) developed HCC after 10–15 years, and 3 (7%) developed HCC after 15 years. Development of HCC within 5 years after HCV eradication was significantly associated with advanced age (>55 years) at eradication and heavy alcohol consumption (≥80 g/day for 5 years). These findings highlight the need for long-term surveillance for HCC development following HCV eradication.

The incidence of HCC in patients with chronic hepatitis C is well known to correlate with the progression of liver fibrosis. In the present study, five of the six patients who had a fibrosis score of F4 developed HCC within 5 years after HCV eradication, suggesting that severe liver fibrosis may be a risk factor for the early development of HCC. Therefore, despite achieving HCV eradication, patients with severe liver fibrosis, as well as those with HCV infection, should receive surveillance for HCC development.

Other factors previously found to be associated with HCC in patients with HCV eradication after IFN therapy were advanced age [26, 27], heavy alcohol consumption, and male sex [1, 5, 28–31], of which the former two were

Table 6 Univariate analysis showing factors associated with radical treatment

Variable	Radical treatment ($n = 26$)	Non-radical treatment ($n = 15$)	P value
Sex (male/female)	21/5	14/1	0.388
Age at HCV eradication (years, ≥55/<55)	22/4	9/6	0.130
Body mass index (kg/m^2, ≥25/<25)	10/16	6/9	1.000
Diabetes mellitus (with/without)	6/20	7/8	0.086
Hypertension (with/without)	11/15	7/8	1.000
Alcohol intake (with/without)	14/12	9/6	0.754
Platelet count (×10^4/μl, <15/≥15)	15/11	6/9	0.341
Development of HCC[a] (years, <5/≥5)	16/10	4/11	0.052
Maximum tumor size (mm, ≤20/>20)	14/12	3/12	0.050
No. of HCC tumors (single/multiple)	18/8	3/12	0.004
AFP (ng/ml, ≤20/>20)	17/9	3/12	0.009
PIVKA-II (mAU/ml, ≤100/>100)	15/11	3/12	0.025
Regular surveillance (received/not received)	17/9	2/13	0.003

Alcohol intake, ≥80 g/day for more than 5 years; regular surveillance, defined as ultrasonography, dynamic CT, or analysis of serum HCC-specific tumor markers (AFP, PIVKA-II) at least annually after IFN therapy

AFP alpha-fetoprotein, *PIVKA-II* protein induced by vitamin K absence or antagonist

[a] Development of HCC within or more than 5 years after the eradication of HCV

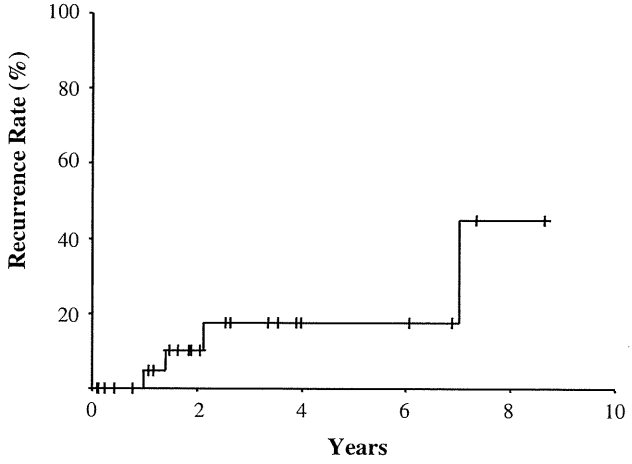

Fig. 3 The recurrence rate of HCC after radical treatment

also confirmed in the present study. In most patients who develop HCC within 5 years after HCV eradication, it is possible that latent HCC may have already been present during IFN therapy or HCV eradication. Patients with the above risk factors should therefore receive careful follow-up and surveillance for early-stage HCC despite showing HCV eradication.

In contrast to the findings within 5 years of HCV eradication, we found no risk factors for the development of HCC more than 10 years after HCV eradication. Although associations between HCC and diabetes mellitus [32–38]; obesity, as indicated by a high BMI; and metabolic syndrome [39–42] have been identified, the incidence of these factors was not significantly higher among patients who developed HCC more than 10 years after HCV eradication in the present study. Half of these patients, however, had diabetes mellitus while few had severe fibrosis, suggesting that metabolic factors are more likely to contribute to the late development of HCC after HCV eradication. Although our study did not identify any risk factors for the development of HCC long after HCV eradiation, this does not preclude the possibility that there is no tendency for HCC development. We therefore consider long-term HCC surveillance after HCV eradication to be necessary.

A better understanding of risk factors for HCC after HCV eradication requires a large prospective study.

Regarding survival in patients who developed HCC after HCV eradication, patients who had received radical treatment; namely, hepatic resection or RFA, had a better 5-year survival rate (91%) than the 30–70% rates for these patients reported previously [43–48]. Further, the underlying liver function reserve in all the patients in our study was chronic hepatitis or Child–Pugh class A cirrhosis. It is clear that a good prognosis is dependent on the maintenance of adequate liver function.

In our study, in contrast with the patients who received radical treatment, the 5-year survival rate in patients who were unable to receive radical treatment was only 25%, and thus significantly worse than that of patients with radical treatment.

Multivariate analysis in our study identified radical treatment as the only independent predictor of overall

Table 7 Clinical characteristics of patients with recurrent HCC after radical treatment

Case	Sex	Age	Alcohol	BMI	Initial HCC								Recurrent HCC							
					Period[a]	Size	No.	Location	Dif	A	F	Tx	Period[b]	Size	No.	Location	Dif	A	F	Tx
1	M	78	+	30	23	15	1	S7	Mod	2	3	HR	12	15	1	S1	NA	NA	NA	TACE, RT
2	M	60	–	25	10	10	1	S8	Well	2	4	HR	17	18	1	S6	Mod	1	2	HR
3	M	55	–	25	42	34	2	S8, S5/8	Mod, poor	2	3	HR	26	18	1	S2	Mod	1	2	HR
4	F	54	–	24	91	18	1	S3	Mod	2	3	HR	85	18	1	S8	Well	1	2	HR

Age, age at HCV eradication (years); alcohol, alcohol intake ≥80 g/day for more than 5 years; BMI, body mass index (kg/m^2); Period[a], period from HCV eradication to development of initial HCC (months); Size, main tumor size (mm); No., number of tumors; Dif, differentiation of tumor; A, activity; F, fibrosis; Tx, treatment; Period[b]; period from primary HCC to development of recurrent HCC (months); TACE, transcatheter arterial chemoembolization; RT, radiation therapy; HR, hepatic resection; NA, not available; Well, well-differentiated type; Mod, moderately differentiated type; Poor, poorly differentiated type

survival, and regular surveillance for HCC as the only predictor of radical treatment. Patients in the present study underwent surveillance for HCC by imaging (ultrasonography and/or dynamic CT) and examination of HCC-specific tumor markers at least annually after HCV eradication. Imaging, analysis of HCC-specific tumor markers, or both, may therefore be necessary on at least an annual basis for detecting HCC in the early stage. A more established protocol for the surveillance of HCC after HCV eradication is necessary.

To our knowledge, this is the first study to report the rate of recurrence of HCC after radical treatment following HCV eradication. Four (15%) of 26 patients who received radical treatment developed tumor recurrence, with both 3- and 5-year recurrence rates being 18%. Cases 1, 2, and 3 were over 55 years of age at HCV eradication, which is also a risk factor for the development of HCC within 5 years after HCV eradication. In addition, these patients also had other risk factors previously associated with HCC development, including male sex (cases 1, 2, and 3), advanced stage 3 or 4 fibrosis before IFN therapy (cases 1, 2, and 3), and heavy alcohol intake (case 1). The time period from the end of IFN therapy to initial HCC development in these three patients ranged from 10 to 42 months, while that from the initial to the recurrent HCC ranged from 12 to 26 months. Although it is difficult to determine whether recurrence was due to intrahepatic metastasis or multicentric occurrence, the latter appears more likely considering the location, pathology, and period until recurrence. Patients with the above risk factors may be at greater risk of recurrence despite receiving radical treatment.

In contrast to the three cases noted above, case 4 was female; age <55 years at HCV eradication; had an 8-year period from the end of IFN therapy to initial HCC development; a 7-year period from the initial to the recurrent HCC; and fewer risk factors associated with HCC development, such as diabetes mellitus, obesity, heavy alcohol intake, or HBV markers. Considering the pathological finding of well-differentiated HCC in this patient, the recurrence in this case was likely of multicentric origin.

In conclusion, we found that, despite HCV eradication, patients with the risk factors of high age at HCV eradication and heavy alcohol intake might be at heightened risk for the development of HCC within 5 years after HCV eradication. In contrast, risk factors for the development of HCC more than 10 years after HCV eradication were uncertain. While receiving radical treatment seems to improve prognosis in HCC patients, it may not decrease the recurrence rate. These findings indicate the need for long-term surveillance for HCC after HCV eradication.

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