Received: 16 October 2020 | Revised: 12 January 2021 | Accepted: 31 January 2021

DOI: 10.1002/ags3.12449

ORIGINAL ARTICLE

AGSurg Annals of Gastroenterological Surgery Open Access WILEY

# Treatment of intrahepatic recurrence after hepatectomy for hepatocellular carcinoma

Michinori Matsumoto | Katsuhiko Yanaga | Hiroaki Shiba | Shigeki Wakiyama | Taro Sakamoto | Yasuro Futagawa | Takeshi Gocho | Yuichi Ishida | Toru Ikegami

Department of Surgery, The Jikei University School of Medicine, Tokyo, Japan

**Correspondence**
Michinori Matsumoto, Department of Surgery, The Jikei University School of Medicine, 3-25-8 Nishi-shinbashi, Minato-ku, Tokyo 105-8461, Japan.
Email: mmatsumoto4@jikei.ac.jp

## Abstract

**Background:** Prognostic factors after treatment for intrahepatic recurrent hepatocellular carcinoma (RHCC) after hepatic resection (Hx) are controversial. The current study aimed to examine the impact of treatment modality on the prognosis of intrahepatic RHCC following Hx.

**Methods:** For control of variables, the subjects were 56 patients who underwent treatment for intrahepatic RHCC, three or fewer tumors, each measuring ≤3 cm in diameter without macroscopic vascular invasion (MVI), between 2000 and 2011. Retreatment consisted of repeat Hx (n = 23), local ablation therapy (n = 11) and transarterial chemoembolization or transcatheter arterial infusion (TACE/TAI) (n = 22). We retrospectively investigated the relation between type of treatment for RHCC and overall survival (OS) as well as disease-free survival (DFS).

**Results:** In multivariate (MV) analysis, the poor prognostic factors in DFS after retreatment consisted of disease-free interval (DFI) (≤1.5 y) ($P = .011$), type of retreatment (TACE/TAI) ($P = .002$), age (<65 y old) ($P = .0022$), perioperative RBC transfusion ($P = .025$), while those in OS after retreatment were DFI (≤1.5 y) ($P < .0001$). In evaluation of stratification for type of retreatment, DFS in the repeat Hx group was significantly better than those in the local ablation therapy group or the TACE/TAI group ($P = .023$ or $P < .0001$, respectively).

**Conclusions:** DFI (≤1.5 y) was an independent poor prognostic factor in both DFS and OS, and repeat Hx for intrahepatic RHCC, few in number and size without MVI, seems to achieve the most reliable local control.

KEYWORDS

hepatectomy, hepatocellular carcinoma, radiofrequency ablation, recurrence, retreatment

## 1 | INTRODUCTION

Remarkable advances in surgical procedures and imaging modalities have improved the outcome of patients with hepatocellular carcinoma (HCC).[1] However, the long-term prognosis remains unsatisfactory because of a high incidence of recurrence even after curative resection of HCC, with a 5-y actuarial recurrence rate of more than 80%.[2,3] The most common site of recurrence is the remnant liver, comprising 85%–90% of initial recurrence sites.[4] For further improvement of therapeutic outcome, the choice of method to treat intrahepatic recurrence is important.

Repeat hepatectomy (Hx) has been reported as the most effective treatment for intrahepatic recurrent HCC (RHCC) after initial Hx, and 5-y survival after repeat Hx, ranged from 56%–69%.[5,6] However, repeat Hx accounts for 10%–50% of RHCC after Hx, because indications for repeat Hx are limited by several factors, including remnant liver function and location, size, and number of tumors.[6,7] Clinical practice guidelines for HCC by the Liver Cancer Study Group of Japan (LCSGJ) showed that a treatment policy for recurrent HCC should be decided based on the same criteria as those for primary HCC; Hx is a standard treatment, and in particular, repeat Hx is advisable for patients with single HCC with good liver function (noncirrhotic liver or Child–Pugh class A).[3] However, optimal selection of therapeutic modality including repeat Hx for RHCC, and risk factors for poor therapeutic outcome, have not been fully investigated.[2,7,8] On the other hand, various effective treatments such as local ablation therapy including ablation and percutaneous ethanol injection therapy (PEIT), or transarterial chemoembolization or transcatheter arterial infusion (TACE/TAI), are available for RHCC.[1] However, stratification for type of treatments for RHCC in relation to prognosis has rarely been analyzed by multivariate (MV) analysis in any past reports.[7,9,10]

The current study aimed to examine the impact of three types of treatment modality on the prognosis and recurrence following Hx for intrahepatic RHCC using MV analysis.

## 2 | PATIENTS AND METHODS

From January 2000 to December 2011, 186 patients with HCC underwent initial Hx at the Department of Surgery, Jikei University Hospital, Tokyo, Japan. By excluding 10 patients with concomitant other malignancies, 61 patients without HCC recurrence and 13 patients with extrahepatic recurrence, the remaining 102 patients with intrahepatic recurrence alone were studied (Figure 1). Of these, treatment for RHCC consisted of repeat Hx in 29, local ablation therapy (LAT) in 15 including two combined therapy of radiofrequency ablation (RFA) and PEIT, repeat Hx and RFA in three, TACE/TAI in 49, and best supportive care (BSC) in six patients. In order to evaluate useful treatment for intrahepatic recurrence of HCC, we excluded 12 patients (combined therapy in three, BSC in six, lack of indocyanine green [ICG] test data in one, and lost to follow-up in two patients), and analyzed the remaining 90 patients retrospectively (Figure 1). Additionally, 56 patients with three or fewer tumors each measuring ≤3 cm in diameter without macroscopic vascular invasion (MVI) were analyzed retrospectively (Figure 1).

The treatment algorithm for HCC was established based on the five factors of hepatic functional reserve, extrahepatic metastasis, vascular invasion, tumor number, and tumor size.[3] Liver function was evaluated based on the Child–Pugh classification. When Hx was being considered, a final decision was made based on liver damage grade,[11] which included ICG-R15.

The indications for Hx were based on an algorithm that included the presence or absence of ascites, serum total bilirubin levels, and results of ICG-R15.[3] It was desirable to perform Hx for up to three tumors located solely in the liver, regardless of tumor size. Multiple tumors were removed by en bloc or multiple Hx when the liver function was good. The use of blood products and the dose were determined in the way we described previously.[12] The tumor staging was based on TNM stage classified by LCSGJ.[11] The RHCC is assessed based on diagnostic imaging findings. The algorithm of treatment for RHCC after Hx was the same treatment algorithm used for primary HCC, which recommended Hx, percutaneous ablation, and TACE in that order for patients who have indications for all three treatment modalities.[3] LAT was considered for patients with Child–Pugh class A or B, up to three tumors, and tumor diameter ≤3 cm if the RHCC was judged unresectable or patients refused Hx.[3] However, LAT was not indicated for patients with RHCC near the porta hepatis or adjacent to other organs because of the potential for complications such as bile duct injury, local recurrence due to insufficient margin, and gastrointestinal perforation. If neither Hx nor LAT was judged applicable, TACE was selected in almost all patients.

First, oncological factors, liver function, recurrence pattern, and type of treatment for RHCC were reviewed and univariate (UV) and MV analyses were performed to determine the prognostic predictors after the recurrence. The factors studied were the following 17 factors: age, gender, type of hepatitis virus, Child–Pugh classification, ICG-R15, type of resection, perioperative blood transfusion of red blood cells (RBC), maximum diameter of tumors, number of tumors, pathological portal or venous invasion, pathological liver cirrhosis at the initial Hx, disease-free interval (DFI), Child–Pugh classification, maximum diameter of tumors, number of tumors, MVI, type of treatment after recurrence. A cutoff value of DFI was determined by a receiving operating curve (ROC) of DFI, which predicted prognosis based on overall survival (OS) and disease-free survival (DFS). Combined therapy with RFA and PEIT was assigned to the LAT group based on the past report.[13]

Second, oncological factors, liver function at the first Hx, recurrence pattern, and type of treatment for the patients with three or fewer tumors each measuring ≤3 cm in diameter without MVI were reviewed and UV and MV analyses were performed to determine the prognostic predictors after recurrence. The factors consisted of

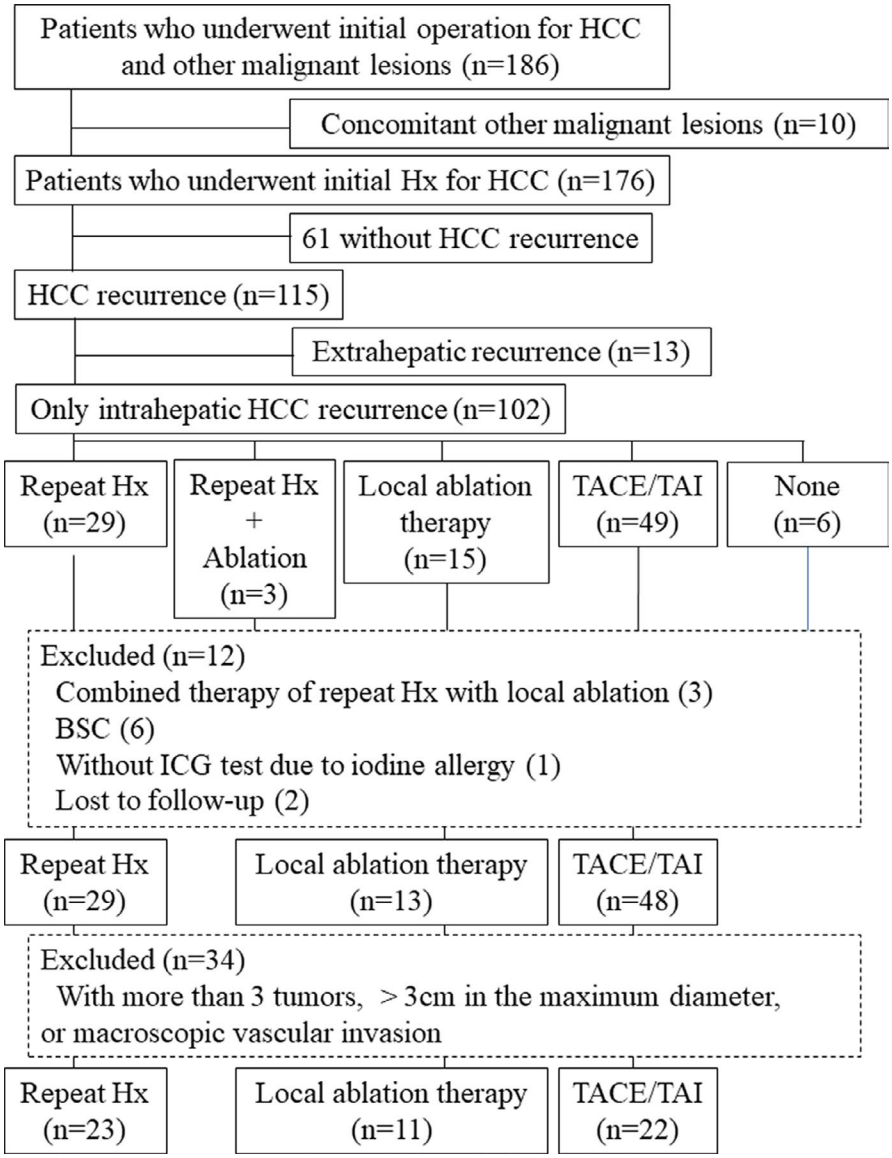


**FIGURE 1** Flow diagram describing patient selection process. HCC, hepatocellular carcinoma; Hx, hepatectomy; BSC, best supportive care; TACE/TAI, transarterial chemoembolization or transcatheter arterial infusion; ICG, indocyanine green

15 factors excluding maximum diameter of tumors and MVI after recurrence from the first analysis.

Third, re-recurrence pattern and type of treatment for re-recurrent HCC (RRHCC) after treatment for the RHCC with three or fewer tumors each measuring ≤3 cm in diameter without MVI were reviewed.

Fourth, we analyzed patient characteristics between two groups, namely, short DFI (≤1.5 y) and long DFI (1.5 y<).

This retrospective study was approved by the Ethics Committee of the Jikei University School of Medicine (27-177 (8062)).

### 2.1 | Statistical analysis

Continuous data were expressed as the median and range, and analyzed by the Mann–Whitney *U* test between two groups and by the Kruskal–Wallis test among three groups. Categorical data were compared by the chi-square test. The accuracy of DFI for prognosis was determined by calculating the area under the curve from the corresponding ROC (AUROC). UV analyses of DFS and OS were performed using the log-rank test. MV analysis, including all variables with *P*-values < .05 in UV analysis, was performed by a stepwise backward procedure until all variables remaining in the model were significant. All *P*-values were considered statistically significant when the associated probability was less than .05 using the Statistical Package for Social Sciences (SPSS 26.0 for Windows, Armonk, NY).

## 3 | RESULTS

### 3.1 | Clinical patient characteristics

Table 1 lists the clinical variables of the 90 patients with intrahepatic RHCC and the clinical variables of the each secondary treatment group. The median age was 67 y (range, 29–84 y old), and 81

**TABLE 1** Characteristics of the 90 patients with intrahepatic metastases between the three retreatment groups

| Variable | All n = 90 | Repeat Hx n = 29 | Local ablation therapy n = 13 | TACE/TAI n = 48 | *P*-value |
|---|---|---|---|---|---|
| Age upon recurrence (y) | 67 (29-84) | 66 (29-84) | 66 (39-77) | 67 (38-82) | 0.346 |
| Gender (male:female) | 81:9 | 25:4 | 13:0 | 43:5 | 0.383 |
| Virus infection (B : C : NBNC) | 21:42:27 | 9:12:8 | 4:6:3 | 8:24:16 | 0.611 |
| Factor at the initial Hx. | | | | | |
| Child–Pugh classification grade (A:B) | 82:8 | 28:1 | 11:2 | 43:5 | 0.391 |
| ICG-R15 (%) | 15 (3-53) | 11 (4-44) | 12 (7-51) | 16 (3-53) | 0.041 |
| Liver damage (A:B) | 63:27 | 26:3 | 7:6 | 30:18 | 0.016 |
| Type of Hx (anatomical:partial) | 38:52 | 13:16 | 9:4 | 16:32 | 0.063 |
| Perioperative RBC transfusion (yes:no) | 19:71 | 4:25 | 2:11 | 13:35 | 0.33 |
| Maximum diameter of tumors (cm) | 3.0 (0.9-18.5) | 3.0 (0.9-10.5) | 2.0 (1.5-9.6) | 3.4 (1.1 18.5) | 0.052 |
| Number of tumors (solitary:multiple) | 69:21 | 25:4 | 8:5 | 36:12 | 0.201 |
| Pathological portal or venous invasion (yes:no) | 72:18 | 6:23 | 0:13 | 12:36 | 0.135 |
| Pathological liver cirrhosis (yes:no) | 47:43 | 16:13 | 7:6 | 24:24 | 0.9 |
| TNM stage classified by LCSGJ (I:II:III:IVA) | 18:38:29:5 | 6:10:13:0 | 5:4:4:0 | 7:21:15:5 | 0.25 |
| Factor upon the recurrence | | | | | |
| Disease-free interval (y) | 1.90 (0.15-11.33) | 2.51 (0.45-8.80) | 1.60 (0.35-5.38) | 1.62 (0.15-11.33) | 0.086 |
| Child–Pugh classification grade (A:B:C) | 74:15:1 | 26:3:0 | 10:3:0 | 38:9:1 | 0.679 |
| Maximum diameter of recurrent tumors (cm) | 2.0 (0.5-11.5) | 2.0 (1.0-11.5) | 1.8 (0.7-3.2) | 2.0 (0.5-7.3) | 0.364 |
| Number of recurrent tumors (solitary: multiple) | 43:47 | 21:8 | 9:4 | 13:35 | <0.0001 |
| Macroscopic vascular invasion (yes: no) | 5:85 | 3:26 | 0:13 | 2:46 | 0.331 |

Abbreviations: Hx, hepatectomy; ICG-R15, the retention rate of indocyanine green at 15 min; LCSGJ, Liver Cancer Study Group of Japan; RBC, red blood cells; TACE/TAI, transarterial chemoembolization or transcatheter arterial infusion.

patients (90%) were male. Hepatitis B virus antigen and hepatitis C virus antibody were positive in 21 (23%) and 42 (47%) patients, respectively, and both were negative in the other 27 patients (30%). The median follow-up period after the initial Hx for primary HCC and after first Hx for RHCC was 7.4 y (range 0.4–15.4 y) and 3.6 y (0.1–12.5 y), respectively. The median DFI was 1.9 y (0.2–11.3 y). The clinical variables among each of the three types of retreatment groups are also summarized in Table 1. As expected, ICG-R15 at the initial Hx was significantly better in the repeated Hx and LAT groups than that of the TACE/TAI group. Patients with multiple RHCC of the TACE/TAI group were statistically greater than that of the repeated Hx and LAT groups. The clinical variables of each retreatment group for the patients with three or fewer tumors each measuring ≤3 cm in diameter without MVI were reviewed and

**TABLE 2** Characteristics of the 56 patients with intrahepatic metastases between the three retreatment groups

| Variable | Repeat Hx n = 23 | Local ablation therapy n = 11 | TACE/TAI n = 22 | *P*-value | Hx vs L *P*-value | L vs T *P*-value | T vs Hx *P*-value |
|---|---|---|---|---|---|---|---|
| Age upon recurrence (y) | 66 (55-84) | 67 (42-79) | 65.5 (38-82) | 0.783 | 0.612 | 0.51 | 0.847 |
| Gender (male:female) | 20:3 | 11:0 | 18:4 | 0.328 | 0.21 | 0.131 | 0.634 |
| Virus infection (B:C:NBNC) | 7:9:7 | 2:6:3 | 8:8:6 | 0.832 | 0.654 | 0.504 | 0.914 |
| Factor at the initial Hx. | | | | | | | |
| Child–Pugh classification grade (A:B) | 22:1 | 9:2 | 19:3 | 0.404 | 0.183 | 0.731 | 0.274 |
| ICG-R15 (%) | 11 (4-44) | 12 (7-51) | 13 (3-53) | 0.575 | 0.513 | 0.836 | 0.316 |
| Liver damage (A:B) | 20:3 | 6:5 | 16; 6 | 0.118 | 0.037 | 0.296 | 0.233 |
| Type of Hx (anatomical:partial) | 9:14 | 7:4 | 7:15 | 0.209 | 0.18 | 0.081 | 0.608 |
| Perioperative RBC transfusion (yes:no) | 4:19 | 1:10 | 5:17 | 0.626 | 0.523 | 0.338 | 0.655 |
| Maximum diameter of tumors (cm) | 3.2 (0.9-10.5) | 2.0 (1.5-9.6) | 2.75 (1.1-9.0) | 0.154 | 0.084 | 0.154 | 0.351 |
| Number of tumors (solitary:multiple) | 19:4 | 8:3 | 18:5 | 0.775 | 0.505 | 0.547 | 0.945 |
| Pathological portal or venous invasion (yes:no) | 3:20 | 0:11 | 5:17 | 0.208 | 0.21 | 0.086 | 0.396 |
| Pathological liver cirrhosis (yes:no) | 16:7 | 6:5 | 11:11 | 0.389 | 0.391 | 0.805 | 0.181 |
| TNM stage classified by LCSGJ (I:II:III:IVA) | 5:11: 7:0 | 5:4:2:0 | 4:10:6:2 | 0.414 | 0.356 | 0.335 | 0.529 |
| Factor upon the recurrence | | | | | | | |
| Disease-free interval (y) | 2.51 (1.48-5.71) | 1.83 (0.35-5.38) | 2.56 (0.37-9.38) | 0.318 | 0.106 | 0.355 | 0.691 |
| Disease-free interval (1.5 y <:≤1.5 y) | 22:1 | 7:4 | 14:8 | 0.02 | 0.014 | 1 | 0.007 |
| Child–Pugh classification grade (A:B) | 20:3 | 8:3 | 18:4 | 0.598 | 0.309 | 0.547 | 0.634 |
| Maximum diameter of recurrent tumors (cm) | 1.8 (1.0-2.6) | 1.8 (0.7-2.5) | 2.0 (0.5-3.0) | 0.744 | 0.513 | 0.486 | 0.945 |
| Number of recurrent tumors (solitary:multiple) | 16:7 | 8:3 | 11:11 | 0.294 | 0.85 | 0.213 | 0.181 |

Abbreviations: Hx, hepatectomy; ICG-R15, the retention rate of indocyanine green at 15 min; LCSGJ, Liver Cancer Study Group of Japan; local ablation therapy vs TACE/TAI, L vs T; RBC, red blood cells; repeat Hx vs local ablation therapy, Hx vs L; TACE/TAI vs repeat Hx, T vs Hx; TACE/TAI, transarterial chemoembolization or transcatheter arterial infusion.

are summarized in Table 2. There was no significantly difference of each variable among the three groups. However, repeat Hx was indicated for patients who were in a better condition than LAT in grade of liver damage at the initial Hx ($P = .037$) and patients who were in a better condition than LAT or TACE/TAI in DFI ($P = .014$ and 0.007, respectively).

## 3.2 | Cutoff value of DFI using ROC

The cutoff value of DFI was determined by a ROC of DFI, which predicted prognosis based on OS and DFS. DFI yielded high AUROC with a level of 0.783 at a cutoff value of 1.53 ($P < .0001$, sensitivity; 0.863, 1 - specificity; 0.333) and with a level of 0.709 at a cutoff value of 1.53 ($P = .008$, sensitivity; .941, 1 - specificity; .562), respectively, which were the same value.

## 3.3 | Variables associated with OS as well as DFS after initial Hx for intrahepatic RHCC in UV and MV analyses

Table 3 shows the relationship between the clinicopathological variables and DFS or OS after initial Hx for intrahepatic RHCC. In UV analysis, DFS was significantly poorer in patients with perioperative RCC transfusion ($P = .0368$), DFI ≤ 1.5 y ($P < .0001$) and multiple tumors at first recurrence ($P = .0013$), while it was significantly better in the patients with repeat Hx than those with the

**TABLE 3** Variables associated with DFS and OS after initial Hx for RHCC in UV and MV analyses

| | | | DFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | UV analysis | | MV analysis | | UV analysis | | MV analysis | |
| | | | HR | | HR | | HR | | HR | |
| Variable | | No. of patients | (95% CI) | *P*-value | (95% CI) | *P*-value | (95% CI) | *P*-value | (95% CI) | *P*-value |
| | Age (y) | | 0.6898 | .1185 | | | 1.167 | .6415 | | |
| | 65≦ | 59 | (0.4044-1.103) | | | | (0.6134-2.215) | | | |
| | <65 | 31 | | | | | | | | |
| | Gender | | 1.454 | .3740 | | | 1.331 | .7264 | | |
| | Female | 9 | (0.6765-2.851) | | | | (0.4729-3.744) | | | |
| | Male | 81 | | | | | | | | |
| | Virus infection | | | .9657 | | | | .7757 | | |
| | B | 21 | 0.9411 | .8529 | | | 0.8088 | .6312 | | |
| | | | (0.4932-1.793) | | | | (0.3347-1.932) | | | |
| | C | 42 | 0.964 | .8942 | | | 0.8511 | .6613 | | |
| | | | (0.5541-1.672) | | | | (0.3922-1.797) | | | |
| | NBNC | 27 | | | | | | | | |
| Factor at the initial Hx. | Child-Pugh | | 1.682 | .1832 | | | 2.212 | .119 | | |
| | B | 8 | (0.7357-5.133) | | | | (0.7510-13.71) | | | |
| | A | 82 | | | | | | | | |
| | ICG-R15 (%) | | 1.491 | .1067 | | | 2.158 | .0283 | 2.29 | .043 |
| | 10< | 60 | (0.9252-2.365) | | | | (1.094-3.892) | | (1.025-5.117) | |
| | ≦10 | 30 | | | | | | | | |
| | Type of Hx | | 0.7242 | .1829 | | | 1.805 | .0607 | | |
| | Anatomical | 38 | (0.4564-1.158) | | | | (0.9741-3.579) | | | |
| | Partial | 52 | | | | | | | | |
| | Perioperative RBC Tx | | 1.741 | .0368 | | | 1.475 | .2689 | | |
| | Present | 19 | (1.050-3.695) | | | | (0.7168-3.344) | | | |
| | Absent | | | | | | | | | |
| | Max diameter of tumor | 71 | 1.057 | 0.8564 | | | 1.846 | 0.087 | | |
| | 5 cm< | 20 | (0.5743-1.951) | | | | (0.9016-5.053) | | | |
| | ≦5 cm | 70 | | | | | | | | |
| | Number of tumor | | 1 | .9992 | | | 1.815 | .0863 | | |
| | Multiple | 21 | (0.5664-1.767) | | | | (0.9083-4.688) | | | |
| | Solitary | 69 | | | | | | | | |

(Continues)

**TABLE 3** (Continued)

| Variable | | No. of patients | DFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | UV analysis | | MV analysis | | UV analysis | | MV analysis | |
| | | | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| | Pathological pv or vv | | 1.443 | .1910 | | | 2.804 | .0015 | 3.878 | .001 |
| | Present | 18 | (0.8150-2.827) | | | | (1.736-10.01) | | (1.774-8.476) | |
| | Absent | 72 | | | | | | | | |
| | Pathological LC | | 1.157 | .5322 | | | 1.046 | .8876 | | |
| | Present | 47 | (0.7290-1.851) | | | | (0.5581-1.962) | | | |
| | Absent | 43 | | | | | | | | |
| Factor upon the recurrence | DFI | | 2.959 | <.0001 | 2.854 | <.0001 | 5.893 | <.0001 | 5.13 | <.0001 |
| | ≤1.5 y | 33 | (2.493-7.853) | | (1.701-4.792) | | (4.494-19.03) | | (2.563-10.268) | |
| | 1.5 y< | 57 | | | | | | | | |
| | Child-Pugh | | 1.261 | .4580 | | | 1.819 | .1427 | | |
| | B or C | 16 | (0.6604-2.532) | | | | (0.7787-5.915) | | | |
| | A | 74 | | | | | | | | |
| | Max diameter of tumor | | 1.297 | 0.4056 | | | 1.907 | 0.0966 | | |
| | 3 cm< | 13 | (0.6779-2.636) | | | | (0.8653-6.004) | | | |
| | ≦3 cm | 77 | | | | | | | | |
| | Number of tumor | | 2.088 | .0013 | | | 2.942 | .0010 | | |
| | Multiple | 47 | (1.379-3.559) | | | | (1.549-5.499) | | | |
| | Solitary | 43 | | | | | | | | |
| | MVI | | 1.723 | .2312 | | | 3.43 | .0121 | | |
| | Present | 5 | (0.6408-6.493) | | | | (1.676-58.56) | | | |
| | Absent | 85 | | | | | | | | |
| | Type of treatment | | | <.0001 | | <.0001 | | .0014 | | .035 |
| | TACE/TAI | 48 | 3.794 | <.0001 | 4.204 | <.0001 | 3.91 | .0004 | 3.801 | .01 |
| | | | (2.896-8.212) | | (2.253-7.844) | | (1.786-6.996) | | (1.374-10.516) | |
| | Local ablation therapy | 13 | 2.261 | .0234 | 1.606 | .225 | 2.993 | .0319 | 2.857 | .116 |
| | | | (1.152-6.348) | | (0.747-3.453) | | (1.192-16.26) | | (0.772-10.576) | |
| | Repeat Hx | 29 | | | | | | | | |

Abbreviations: CI, confidence interval; DFI, disease-free interval; DFS, disease-free survival; HR, hazard ration; Hx, hepatectomy; ICG-R15, the retention rate of indocyanine green at 15 minutes; LC, liver cirrhosis; Max, maximum pv or vv, portal or venous invasion; MV, multivariate analysis; MVI, macroscopic vascular invasion; OS, overall survival; RCC, red blood cells; RHCC, recurrent hepatocellualr carcinoma; TACE/TAI, transarterial chemoembolization or transcatheter arterial infusion; Tx, transfusion; UV, univariate analysis. [Correction added on 25 March 2021, after online publication: the values in the table are aligned correctly.]

LAT or TACE/TAI groups ($P < .0001$). In MV analysis, DFI ≤ 1.5 y was an independent predictor of poor DFS ($P < .0001$), while type of treatment for recurrent RHCC was an independent predictor of good DFS ($P < .0001$). However, there were no significant differences of DFS between repeat Hx and LAT groups for RHCC by MV analysis. Figure 2A shows the comparison of DFS rates according to types of treatment for intrahepatic RHCC. The 1-, 3-, and 5-y DFS rates were 65.5%, 43.4%, and 43.4% for the repeat Hx group, 30.8%, 15.4%, and 0% for the LAT group, 15.6%, 0%, and 0% for the TACE/TAI group, respectively. The DFS rate of the patients with a repeat Hx was significantly higher than those with local therapy or TACE/TAI ($P = .0234$ or $P < .0001$, respectively).

On the other hand, in UV analysis OS was poorer in patients with 10% < ICG-R15 ($P = .0283$), pathological portal or hepatic vein invasion at initial Hx ($P = .0015$), DFI ≤ 1.5 y ($P < .0001$), multiple tumors ($P = .0010$), and MVI ($P = .0121$) at recurrence, while significantly better in the patients with repeat Hx for RHCC than those with LAT or TACE/TAI ($P = .0014$). In MV analysis, DFI ≤ 1.5 y ($P < .0001$), 10% < ICG-R15 ($P = .043$) and pathological portal or hepatic vein invasion at initial Hx ($P = .001$) were independent predictors of poor OS, while type of treatment for RHCC was an independent predictor of good OS ($P = .035$). However, there were no significant differences in OS between repeat Hx and LAT for RHCC by MV analysis. Figure 2B shows the comparison of OS rates according to types of treatment for intrahepatic RHCC. The 1-, 3-, and 5-y OS rates were 93.1%, 89.7%, and 84.9% for the repeat Hx group, 84.6%, 74.0%, and 74.0% for the LAT group, 86.5%, 59.1%, and 43.3% for the TACE/TAI group, respectively. The OS rate of the patients with repeat Hx was significantly

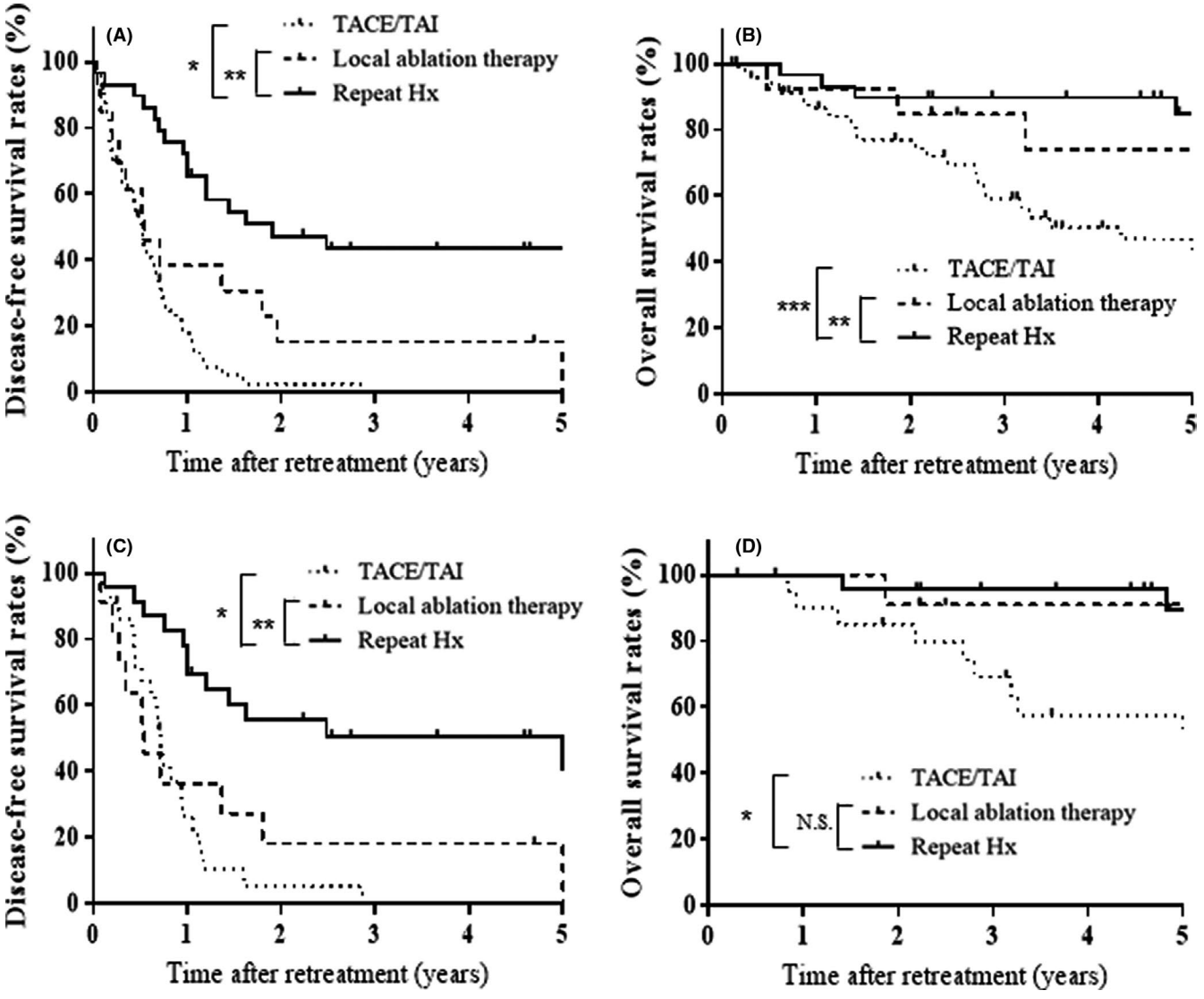


**FIGURE 2** Disease-free survival (DFS) and overall survival (OS) of each type of treatment for intrahepatic recurrent hepatocellular carcinoma (RHCC) (A,B) and for intrahepatic RHCC, three or fewer tumors each measuring ≤3 cm in diameter without macroscopic vascular invasion (C,D). Repeat hepatic resection (Hx) group was associated with significantly better DFS (A) or OS (B) than the other groups. As to the few and small RHCC, repeat Hx group was associated with significantly better DFS than the other groups (C). OS rates of repeat Hx group were significantly better than that of transarterial chemoembolization or transcatheter arterial infusion (TACE/TAI) group (D). *$P <$ .0001, **$P < .05$, and ***$P < .001$. NS, not significant

higher than those with LAT or TACE/TAI ($P$ = .0319 or $P$ = .0004, respectively).

### 3.4 | Variables associated with OS as well as DFS after initial Hx for intrahepatic RHCC, three or fewer tumors each measuring ≤3 cm in diameter without MVI, in UV and MV analyses

Table 4 shows the relationship between the clinicopathological variables and DFS or OS after initial Hx for intrahepatic RHCC, three or fewer tumors each measuring ≤3 cm in diameter without MVI. In UV analysis, DFS was significantly poorer in patients with younger age (<65 y old) ($P$ = .0187), perioperative RBC transfusion ($P$ = .0222) or DFI ≤ 1.5 y ($P$ = .0001), while repeat Hx for the RHCC was an independent predictor of good DFS ($P$ =.0002). In MV analysis, DFI ≤ 1.5 y was an independent predictor of poor DFS ($P$ =.011), while repeat Hx for the RHCC was an independent predictor of good DFS ($P$ =.002). Furthermore, DFS was significantly better in patients with repeat Hx for the RHCC than those with LAT ($P$ =.023) or TACE/TAI ($P$ < .0001) by MV analysis. Figure 2C shows the comparison of DFS rates according to types of treatment for RHCC, three or fewer tumors each measuring ≤3 cm in diameter without MVI. The 1-, 3-, and 5-y DFS rates were 69.6%, 50.6%, and 40.5% for the repeat Hx group, 36.4%, 18.2%, and 18.2% for the LAT group, 26.3%, 0%, and 0% for the TACE/TAI group, respectively. The DFS rate of the patients with repeat Hx was significantly higher than those with LAT or TACE/TAI ($P$ = .0175 or $P$ < .0001, respectively).

On the other hand, in UV analysis OS was significantly poorer in patients with DFI ≤ 1.5 y ($P$ = .0001) and Child–Pugh classification grade B at recurrence ($P$ = .0301), while repeat Hx for the RHCC was an independent predictor of good OS ($P$ = .0302). In MV analysis, DFI ≤ 1.5 y was an independent predictor of poor OS ($P$ < .0001) (Table 4), while type of treatment for the few and small RHCC was not an independent prognostic factor in multivariate analysis for OS but showed a trend toward correlation with OS ($P$ = .078). Figure 2D shows the comparison of OS rates according to types of treatment for the RHCC, three or fewer tumors each measuring ≤3 cm in diameter without MVI. The 1-, 3-, and 5-y OS rates were 100%, 100%, and 89.3% for the repeat Hx group, 100%, 90.9%, and 90.9% for the LAT group, 90.0%, 69.1%, and 57.6% for the TACE/TAI group, respectively. The OS rate of patients with repeat Hx was significantly higher than those with LAT or TACE/TAI ($P$ = .0956 or $P$ = .0102, respectively).

### 3.5 | Re-recurrence pattern and type of treatment for RRHCC after treatment for the RHCC, three or fewer tumors each measuring ≤3 cm in diameter without MVI

Forty patients had RRHCC after retreatment among 56 patients with the RHCC (71%). Among the three types of treatment for RHCC, there was no significant difference in DFI before the RRHCC, re-recurrence pattern and type of treatment for RRHCC (Table 5). Of the patients with the RRHCC after repeat Hx, local therapy, and TACE/TAI, 5, 4, and 15 patients had TACE/TAI, respectively (33%, 44%, and 79%, respectively).

### 3.6 | Univariate analysis of patient characteristics in relation to DFI

Table 6 demonstrates the relationship between clinicopathological variables and DFI. In univariate analysis, pathological portal or venous invasion ($P$ = .016), portal vein invasion ($P$ = .020), number of tumor ($P$ = .026), advanced TNM stage by LCSGJ ($P$ = .002) of initial HCC, number of tumor ($P$ = .037), and macroscopic vascular invasion ($P$ = .002) of RHCC were significantly associated with short DFI. On the other hand, in univariate analysis for the 56 patients, DFI ≤ 1.5 y was significantly related with worse hepatic functional reserve at recurrence ($P$ = .027).

## 4 | DISCUSSION

HCC usually recurs repeatedly in the remnant liver, for which locoregional treatment is attempted unless liver function has deteriorated. Previous studies demonstrated the benefit of aggressive treatment with repeat Hx or ablation after RHCC.[6,14,15] Several studies showed better survival rates after repeat Hx than those after nonsurgical treatment such as RFA or TACE.[5,15,16] Although more than one effective method of treatment are available for RHCC, stratification for type of treatment for RHCC has rarely been analyzed by MV analysis.[14,15,17,18] To the best of our knowledge, this is the second to report that type of treatment for intrahepatic recurrence of HCC was an independent recurrent factors in DFS[14] and the first to report that DFS was significantly better in patents with repeat Hx than LAT or TACE for RHCC after Hx by MV analysis.

Some reports concerning the association between prognosis and treatments for RHCC after Hx report that treatment modalities for RHCC are prognostic factors.[14,17,18] A study that compared Hx with RFA for RHCC after Hx revealed comparable results between the two treatment modalities.[19] However, TACE was found to be inferior to Hx and RFA,[17] and better prognosis was found after Hx than TACE in meta-analyses.[15,20] Erridge et al reported in a meta-analysis that important negative prognostic factors for RHCC after Hx were short DFI, multiple hepatic metastases, and large hepatic metastases.[15]

In the current study, MV analysis for the 90 patients with intrahepatic RHCC also revealed that the type of treatment for RHCC was a significantly prognostic and recurrent factor. However, neither DFS nor OS showed a significant difference between repeat Hx and LAT. This might be due to selection bias for retreatment, not only because we performed repeat Hx for RHCC as a first choice if it was resectable and remnant liver function was reserved, but also because the indication for LAT was limited to patients with three or

**TABLE 4** Variables associated with DFS and OS after initial Hx for RHCC, 3 or fewer tumors each measuring 3cm in diameter without MVI, in UV and MV analyses

| | | | DFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | UV analysis | | MV analysis | | UV analysis | | MV analysis | |
| Variable | | No. of patients | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| | Age (y) | | 0.5422 | .0187 | 0.478 | .022 | 1.088 | .8587 | | |
| | 65≦ | 34 | (0.2603-0.9592) | | (0.255-0.897) | | (0.4276-2.774) | | | |
| | <65 | 22 | | | | | | | | |
| | Gender | | 0.7463 | .5729 | | | 0.9606 | .9571 | | |
| | Female | 7 | (0.3064-1.918) | | | | (0.2260-4.086) | | | |
| | Male | 49 | | | | | | | | |
| | Virus infection | | | .7177 | | | | .9750 | | |
| | B | 13 | 1.279 | .5435 | | | 1.02 | .9751 | | |
| | | | (0.5767-2.861) | | | | (0.2887-3.608) | | | |
| | C | 19 | 0.8296 | .6134 | | | 0.8109 | .7222 | | |
| | | | (0.3806-1.755) | | | | (0.2268-2.757) | | | |
| | NBNC | 11 | | | | | | | | |
| Factor at the initial Hx. | Child-Pugh | | 1.916 | .1605 | | | 2.219 | .2697 | | |
| | B | 6 | (0.7127-8.161) | | | | (0.4126-25.21) | | | |
| | A | 50 | | | | | | | | |
| | ICG-R15 (%) | | 1.4 | .2789 | | | 1.422 | .4592 | | |
| | 10< | 34 | (0.7671-2.549) | | | | (0.5645-3.591) | | | |
| | ≦10 | 22 | | | | | | | | |
| | Procedure | | 0.6521 | .1828 | | | 2.38 | .0581 | | |
| | Anatomical | 23 | (0.3613-1.210) | | | | (0.9728-6.800) | | | |
| | Partial | 33 | | | | | | | | |
| | Perioperative RBC Tx | | 2.216 | .0222 | 2.411 | .025 | 1.495 | .4402 | | |
| | Present | 10 | (1.179-7.403) | | (1.118-5.198) | | (0.5004-4.942) | | | |
| | Absent | 46 | | | | | | | | |
| | Max diameter of tumor | | 0.378 | .1581 | | | 1.4717 | .6386 | | |
| | 5 cm< | 6 | (0.1973-1.292) | | | | (0.2766-8.169) | | | |
| | ≦5 cm | 50 | | | | | | | | |

(Continues)

**TABLE 4** (Continued)

| Variable | | No. of patients | DFS | | | | OS | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | UV analysis | | MV analysis | | UV analysis | | MV analysis | |
| | | | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| | Number of tumor | | 0.9418 | .8766 | | | 0.9055 | .8470 | | |
| | Multiple | 11 | (0.4428-2.000) | | | | (0.2730-3.010) | | | |
| | Solitary | 45 | | | | | | | | |
| | Pathological pv or vv | | 1.141 | .7469 | | | 2.659 | .0527 | | |
| | Present | 8 | (0.4931-2.686) | | | | (0.9862-15.91) | | | |
| | Absent | 48 | | | | | | | | |
| | Pathological LC | | 0.8959 | .7215 | | | 1.367 | .5293 | | |
| | Present | 33 | (0.4776-1.662) | | | | (0.5283-3.467) | | | |
| | Absent | 23 | | | | | | | | |
| Factor upon the recurrence | DFI | | 3.213 | .0001 | 2.585 | .011 | 6.138 | <.0001 | 6.401 | <.0001 |
| | ≤1.5 y | 43 | (2.506-15.89) | | (1.242-5.385) | | (4.774-56.12) | | (2.313-17.720) | |
| | 1.5 y< | 13 | | | | | | | | |
| | Child-Pugh | | 1.313 | .5037 | | | 2.944 | .0301 | | |
| | B | 10 | (0.5576-3.318) | | | | (1.181-21.26) | | | |
| | A | 46 | | | | | | | | |
| | Number of tumor | | 1.443 | .2253 | | | 2.276 | .0715 | | |
| | Multiple | 21 | (0.7909-2.760) | | | | (0.9342-6.446) | | | |
| | Solitary | 35 | | | | | | | | |
| | Type of treatment | | | .0002 | | .002 | | .0320 | | .078 |
| | TACE/TAI | 22 | 3.92 | <.0001 | 4.102 | <.0001 | 3.998 | .0102 | 3.851 | .037 |
| | | | (2.816-12.83) | | (1.870-8.999) | | (1.423-12.26) | | (1.088-13.634) | |
| | Local ablation therapy | 11 | 2.598 | .0175 | 2.744 | .023 | 2.957 | .0956 | 1.631 | .525 |
| | | | (1.242-8.701) | | (1.147-6.566) | | (0.8262-20.05) | | (0.361-7.368) | |
| | Repeat Hx | 23 | | | | | | | | |

Abbreviations: CI, confidence interval; DFI, disease-free interval; DFS, disease-free survival; HR, hazard ration; Hx, hepatectomy; ICG-R15, the retention rate of indocyanine green at 15 minutes; LC, liver cirrhosis; Max, maximum pv or vv, portal or venous invasion; MV, multivariate analysis; MVI, macroscopic vascular invasion; OS, overall survival; RCC, red blood cells; RHCC, recurrent hepatocellualr carcinoma; TACE/TAI, transarterial chemoembolization or transcatheter arterial infusion; Tx, transfusion; UV, univariate analysis. [Correction added on 25 March 2021, after online publication: the values in the table are aligned correctly.]

**TABLE 5** Re-recurrence pattern and type of treatment for RRHCC after treatment for the RHCC, three or fewer tumors each measuring ≤3 cm in diameter without MVI

| Variable | Repeat Hx (n = 12) | Local ablation therapy (n = 9) | TACE/TAI (n = 19) | *P*-value |
|---|---|---|---|---|
| DFI until the RRHCC (y) | 0.999 ( 0.121-6.499) | 0.518 (0.077-1.803) | 0.685 (0.110-2.871) | 0.102 |
| Re-recurrence pattern (Intrahepatic:Intrahepatic + MVI:Intrahepatic + Extrahepatic | 11:0:1 | 9:0:0 | 16:2:1 | 0.541 |
| Type of treatment for RRHCC | | | | |
| Repeat Hx: Repeat Hx + RFA: RFA:TACE/TAI:Sorafenib:None | 3:1:2:5:1:1 | 1:0:4:4:0:0 | 1:0:2:15:1:0 | 0.179 |

Abbreviations: DFI, disease-free interval; HCC, hepatocellular carcinoma; Hx, hepatectomy; MVI, macroscopic vascular invasion; RFA, radiofrequency ablation; RHCC, recurrent HCC; RRHCC, re-recurrent HCC; TACE/TAI, transarterial chemoembolization or transcatheter arterial infusion.

fewer tumors and each measuring ≤3 cm in diameter without MVI. Therefore, 56 patients with three or fewer tumors and each measuring ≤3 cm in diameter without MVI out of the 90 patients with RHCC were reanalyzed to minimize the selection bias of tumor stage. As to the significantly better DFS in patients with repeat Hx for RHCC than those with LAT or TACE/TAI, this may be because complete necrosis of tumor by TACE are reported to range between 0%–28%[21] and because Hx removes normal liver parenchyma together with the original tumor and thus eradicate both primary tumor and venous thrombi,[22,23] and LAT sometimes causes an insufficient safety margin or neoplastic seedings.[23] Therefore, repeat Hx for few and small RHCC might achieve the most reliable local control treatment. On the other hand, the type of treatment for the few and small RHCC was not a significant prognostic factor. One of the reasons might be due to no significant difference by minimizing the selection bias of tumor factor (Table 2). Of 40 patients with RRHCC, 37 patients underwent one of the three types of treatment such as Hx, LAT, or TACE/TAI. Kishi et al reported that repeated locoregional treatment, and not the type of treatment for RHCC, is associated with improved patient prognosis after recurrence.[24] Maintenance of liver functional reserve is necessary for repeat locoregional treatment. Actually, in the current study, ICG-R15 was a significant prognostic factor in analyzing the 90 patients with RHCC, while the liver function factor might be not significantly related to the prognosis in the 56 patients because DFI ≤ 1.5 y and liver dysfunction at the recurrence were confounding factors based on Table 6. The present study showed that the optimal treatment for RHCC in terms of prognosis after recurrence seems to be the combination of repeat Hx and LAT.

In the current study, younger age was a significantly poor recurrent factor after retreatment for RHCC, which is few in number and size. Some previous reports have showed that younger patients have a worse prognosis,[25,26] which is consistent with our results. However, those researchers reported that the poorer prognosis is mainly attributable to worse tumor-related indicators, such as larger tumor diameter, later tumor stage, and higher serum AFP concentration. Li et al reported poor OS and DFS of HCC patients aged younger than 60 y with microvascular invasion.[27] The poor prognosis and recurrence in the young age group could be explained by late detection as well as their own aggressive tumor biology, with increased cell division because of a higher mitotic index.[28] However, other studies showed opposite or arbitrary results.[29] For HCC, therefore, the prognosis of young patients remains controversial.

The most frequently proposed independent predictor after retreatment for RHCC after first Hx has been a short DFI.[15] Previous studies suggested that a 1- to 2-y DFI could be an arbitrary cutoff timepoint.[2,5,7,9,10,13,17,20,24] However, these suggested cutoff timepoints were based on subjective estimation rather than objective analysis on a large scale of clinicopathological data. In the current study, DFI of 1.5 y was the optimal cutoff time by ROC curve analysis between DFI and OS or between DFI and DFS, respectively, which coincided. DFI was reported to have the capacity to predict the pattern of RHCC. Previous studies have revealed that intrahepatic metastasis (IM) and multicentric occurrence (MO) are the main types of intrahepatic RHCC.[2,4] IM refers to HCC foci developing from tumor cells that have spread into the remnant liver via portal vein before or during Hx.[2] MO refers to the development of new HCC foci due to the existence of chronic active hepatitis, cirrhosis, or other HCC-relevant risk factors after Hx.[4] Huang et al reported that a DFI of 18 mo after initial resection was a significant cutoff timepoint for differentiating between IM and MO by using ROC curve analysis,[30] which coincided with the current study, and that a DFI of less than or equal to 18 mo and microvascular invasion at repeat Hx were independent adverse prognostic factors for OS after repeat Hx.[30] In the current study, a cutoff time of DFI calculated by ROC curve analysis between DFI and OS or between DFI and DFS ,respectively, 1.5 y, might also differentiate IM from MO because pathological portal vein invasion of initial HCC ($P = .020$) was significantly associated with short DFI (≤1.5 y) in univariate analysis. Theoretically, the type of recurrent HCC from IM (early recurrence) or MO (late recurrence) should be considered in the therapeutic selection for recurrent HCC.

The current study has several limitations. First, this was a retrospective study and the type of treatment was not decided in the randomized settings before recurrence. Selection bias for the choice of treatment for RHCC arose because the treatment policy for RHCC followed the clinical practice guideline for HCC by LCSGJ.[3] Second, the number of patients who underwent repeat Hx or LAT was small, and the survival rate after treatment for recurrence might

**TABLE 6** The relationship between clinicopathological variables and disease-free interval

| | All cases (n = 90) | | | | Cases with three or fewer tumors and each measuring ≤3 cm in diameter without MVI (n = 56) | | | |
|---|---|---|---|---|---|---|---|---|
| | Median (range) or Ratio | | | | Median (range) or Ratio | | | |
| | n = 90 | n = 57 | n = 33 | *P*-value | n = 56 | n = 43 | n = 13 | *P*-value |
| **Variables** | | **1.5 y<** | **≤1.5 y** | | | **1.5 y<** | **≤1.5 y** | |
| Age upon recurrence (y) | 67 (29-84) | 67 (42-84) | 66 (29-82) | 0.471 | 66 (38-84) | 66 (42- 84) | 66 (38-82) | 0.961 |
| Gender (Male:Female) | 81:9 | 53:4 | 28:5 | 0.215 | 49:7 | 39:4 | 10:3 | 0.188 |
| Virus infection (B:C:BC:NBNC) | 21:42:27 | 14:27:16 | 7:15:11 | 0.856 | 17:23:16 | 14:18:11 | 3:5:5 | 0.637 |
| Factor at the initial Hx. | | | | | | | | |
| Child–Pugh classification grade (A:B) | 82:8 | 52:5 | 30:3 | 0.959 | 50:6 | 38:5 | 12:1 | 0.688 |
| ICG-R15 (%) | 15 (3-53) | 14 (4-53) | 16 (3-34) | 0.962 | 12 (3-53) | 13 (4-53) | 8 nn | 0.075 |
| Liver damage (A:B:C) | 63:27 | 42:15 | 21:12 | 0.316 | 42:14 | 32:11 | 10:3 | 0.855 |
| Type of Hx (anatomical:partial) | 38:52 | 21:36 | 17:16 | 0.174 | 23:33 | 17:26 | 6:7 | 0.671 |
| Perioperative RBC transfusion (yes:no) | 19:71 | 11:46 | 8:25 | 0.58 | 10:46 | 6:37 | 4:9 | 0.165 |
| Maximum diameter of tumors (cm) | 3.0 (0.9-18.5) | 3.0 (0.9-13.0) | 3.0 (1.5-18.5) | 0.363 | 2.6 (0.9-10.5) | 2.7 (0.9-10.5) | 2.5 (1.8-9.6) | 0.741 |
| Number of tumors (solitary:multiple) | 21:69 | 9:48 | 12:21 | 0.026 | 45:11 | 35:8 | 10:3 | 0.722 |
| Pathological portal or venous invasion (yes:no) | 18:72 | 7:50 | 11:22 | 0.016 | 8:48 | 5:38 | 3:10 | 0.301 |
| Pathological portal invasion (yes:no) | 14:76 | 5:52 | 9:24 | 0.02 | 5:51 | 3:40 | 2:11 | 0.352 |
| MVI (yes:no) | 3:87 | 1:56 | 2:31 | 0.273 | 0:56 | 0:43 | 0:13 | NA |
| Pathological liver cirrhosis (yes:no) | 47:43 | 29:28 | 18:15 | 0.737 | 33:23 | 25:18 | 8:5 | 0.827 |
| TNM stage classified by LCSGJ (I:II:III:IVA) | 18:38:29:5 | 15:27:15:0 | 3:11:14:5 | 0.002 | 14:25:15:2 | 12:19:12:0 | 2:6:3:2 | 0.062 |
| Factor upon the recurrence | | | | | | | | |
| Disease-free interval (y) | 1.897 (0.151-11.332) | 2.951 (1.570-11.332) | 0.679 (0.151-1.490) | <0.0001 | 2.40 (0.35-9.38) | 2.81 (1.57-9.38) | 0.84 (0.35-1.48) | <0.0001 |
| Child–Pugh classification grade (A:B:C) | 74:15:1 | 50:7:0 | 24:8:1 | 0.129 | 46:10:0 | 38:5:0 | 8:5:0 | 0.027 |
| Maximum diameter of recurrent tumors (cm) | 2.0 (0.5-11.5) | 2.0 (0.5-5.2) | 1.9 (1.0-11.5) | 0.668 | 1.8 (0.5-3.0) | 1.8 (0.5-3.0) | 1.8 (1.0-3.0) | 0.704 |
| Number of recurrent tumors (solitary:multiple) | 43:47 | 32:25 | 11:22 | 0.037 | 35:10:11 | 28:7:8 | 7:3:3 | 0.755 |
| MVI (yes:no) | 5:85 | 0:57 | 5:28 | 0.002 | 0:56 | 0:43 | 0:13 | NA |
| Type of treatment (repeat Hx:local ablation thearpy:TACE/TAI) | 29:13:48 | 25:7:25 | 4:6:23 | 0.008 | 23:11:22 | 22:7:14 | 1:4:8 | 0.02 |

Abbreviations: Hx, hepatectomy; ICG-R15, the retention rate of indocyanine green at 15 min; LCSGJ, Liver Cancer Study Group of Japan; MVI, macroscopic vascular invasion; NA, not available; RBC, red blood cells; TACE/TAI, transarterial chemoembolization or transcatheter arterial infusion.

be underestimated. To confirm the influence of type of treatment on survival after recurrence, large-scale multicenter studies are required.

In conclusion, repeat Hx for patients with intrahepatic RHCC, few in number and size, after initial Hx may improve recurrence-free survival, especially in patients with a longer recurrence-free interval, more than 1.5 y.

## DISCLOSURE

Conflict of Interest: The authors declare no conflicts of interest and received no funding support for this study.

## ORCID

*Michinori Matsumoto* https://orcid.org/0000-0002-5860-1103
*Katsuhiko Yanaga* https://orcid.org/0000-0001-8918-4720
*Hiroaki Shiba* https://orcid.org/0000-0003-0688-2078
*Shigeki Wakiyama* https://orcid.org/0000-0003-0108-7657
*Taro Sakamoto* https://orcid.org/0000-0002-5917-7201
*Yasuro Futagawa* https://orcid.org/0000-0003-1994-6309
*Takeshi Gocho* https://orcid.org/0000-0002-8463-905X
*Yuichi Ishida* https://orcid.org/0000-0002-8065-341X
*Toru Ikegami* https://orcid.org/0000-0001-5792-5045

## REFERENCES

1. Yanaga K. Current status of hepatic resection for hepatocellular carcinoma. J Gastroenterol. 2004;39(10):919–26.
2. Imamura H, Matsuyama Y, Tanaka E, Ohkubo T, Hasegawa K, Miyagawa S, et al. Risk factors contributing to early and late phase intrahepatic recurrence of hepatocellular carcinoma after hepatectomy. J Hepatol. 2003;38(2):200–7.
3. Kokudo N, Takemura N, Hasegawa K, Takayama T, Kubo S, Shimada M, et al. Clinical practice guidelines for hepatocellular carcinoma: the Japan Society of Hepatology 2017 (4th JSH-HCC guidelines) 2019 update. Hepatol Res. 2019;49(10):1109–13.
4. Arii S, Teramoto K, Kawamura T, Okamoto H, Kaido T, Mori A, et al. Characteristics of recurrent hepatocellular carcinoma in Japan and our surgical experience. J Hepato-biliary Pancreat Surg. 2001;8(5):397–403.
5. Shimada M, Takenaka K, Gion T, Fujiwara Y, Kajiyama K, Maeda T, et al. Prognosis of recurrent hepatocellular carcinoma: a 10-y surgical experience in Japan. Gastroenterology. 1996;111(3):720–6.
6. Minagawa M, Makuuchi M, Takayama T, Kokudo N. Selection criteria for repeat hepatectomy in patients with recurrent hepatocellular carcinoma. Ann Surg. 2003;238(5):703–10.
7. Poon RT, Fan ST, Lo CM, Liu CL, Wong J. Intrahepatic recurrence after curative resection of hepatocellular carcinoma: long-term results of treatment and prognostic factors. Ann Surg. 1999;229(2):216–22.
8. Taura K, Ikai I, Hatano E, Fujii H, Uyama N, Shimahara Y. Implication of frequent local ablation therapy for intrahepatic recurrence in prolonged survival of patients with hepatocellular carcinoma undergoing hepatic resection: an analysis of 610 patients over 16 y old. Ann Surg. 2006;244(2):265–73.
9. Liang H-H, Chen M-S, Peng Z-W, Zhang Y-J, Zhang Y-Q, Li J-Q, et al. Percutaneous radiofrequency ablation versus repeat hepatectomy for recurrent hepatocellular carcinoma: a retrospective study. Ann Surg Oncol. 2008;15(12):3484–93.
10. Chen W-T, Chau G-Y, Lui W-Y, Tsay S-H, King K-L, Loong C-C, et al. Recurrent hepatocellular carcinoma after hepatic resection: prognostic factors and long-term outcome. Eur J Surg Oncol. 2004;30(4):414–20.
11. Minagawa M, Ikai I, Matsuyama Y, Yamaoka Y, Makuuchi M. Staging of hepatocellular carcinoma: assessment of the Japanese TNM and AJCC/UICC TNM systems in a cohort of 13,772 patients in Japan. Ann Surg. 2007;245(6):909–22.
12. Shiba H, Ishida Y, Wakiyama S, Iida T, Matsumoto M, Sakamoto T, et al. Negative impact of blood transfusion on recurrence and prognosis of hepatocellular carcinoma after hepatic resection. J Gastrointest Surg. 2009;13(9):1636–42.
13. Shah SA, Cleary SP, Wei AC, Yang I, Taylor BR, Hemming AW, et al. Recurrence after liver resection for hepatocellular carcinoma: risk factors, treatment, and outcomes. Surgery. 2007;141(3):330–9.
14. Wang K, Liu G, Li J, Yan Z, Xia Y, Wan X, et al. Early intrahepatic recurrence of hepatocellular carcinoma after hepatectomy treated with re-hepatectomy, ablation or chemoembolization: a prospective cohort study. Eur J Surg Oncol. 2015;41(2):236–42.
15. Erridge S, Pucher PH, Markar SR, Malietzis G, Athanasiou T, Darzi A, et al. Meta-analysis of determinants of survival following treatment of recurrent hepatocellular carcinoma. Br J Surg. 2017;104(11):1433–42.
16. Tabrizian P, Jibara G, Shrager M, Roayaie S. Recurrence of hepatocellular cancer after resection. Ann Surg. 2015;261:947–955. http://dx.doi.org/10.1097/sla.0000000000000710.
17. Ho CM, Lee PH, Shau WY, Ho MC, Wu YM, Hu RH. Survival in patients with recurrent hepatocellular carcinoma after primary hepatectomy: comparative effectiveness of treatment modalities. Surgery. 2012;151(5):700–9.
18. Umeda Y, Matsuda H, Sadamori H, Matsukawa H, Yagi T, Fujiwara T. A prognostic model and treatment strategy for intrahepatic recurrence of hepatocellular carcinoma after curative resection. World J Surg. 2011;35(1):170–7.
19. Song KD, Lim HK, Rhim H, Lee MW, Kim Y-S, Lee WJ, et al. Repeated hepatic resection versus radiofrequency ablation for recurrent hepatocellular carcinoma after hepatic resection: a Propensity Score Matching Study. Radiology. 2015;275(2):599–608.
20. Wang D-Y, Liu L, Qi X-S, Su C-P, Chen X, Liu XU, et al. Hepatic re-resection versus transarterial chemoembolization for the treatment of recurrent hepatocellular carcinoma after initial resection: a Systematic Review and Meta-analysis. Asian Pac J Cancer Prev. 2015;16(13):5573–8.
21. Chua TC, Liauw W, Saxena A, Chu F, Glenn D, Chai A, et al. Systematic review of neoadjuvant transarterial chemoembolization for resectable hepatocellular carcinoma. Liver Int. 2010;30(2):166–74.
22. Shi M, Guo R-P, Lin X-J, Zhang Y-Q, Chen M-S, Zhang C-Q, et al. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. Ann Surg. 2007;245(1):36–43.
23. Huang J, Yan L, Cheng Z, Wu H, Du L, Wang J, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Ann Surg. 2010;252(6):903–12.
24. Kishi Y, Saiura A, Yamamoto J, Koga R, Seki M, Morimura R, et al. Repeat treatment for recurrent hepatocellular carcinoma: is it validated? Langenbecks Arch Surg. 2011;396(7):1093–100.
25. Mirici-Cappa F, Gramenzi A, Santi V, Zambruni A, Di Micoli A, Frigerio M, et al. Treatments for hepatocellular carcinoma in elderly patients are as effective as in younger patients: a 20-y multicentre experience. Gut. 2010;59(3):387–96.
26. Saneto H, Kobayashi M, Kawamura Y, Yatsuji H, Sezaki H, Hosaka T, et al. Clinicopathological features, background liver disease, and survival analysis of HCV-positive patients with hepatocellular carcinoma: differences between young and elderly patients. J Gastroenterol. 2008;43(12):975–81.
27. Li L, Xu L, Wen T, Wu H, Wang W, Yang J, et al. Poor prognoses of young hepatocellular carcinoma patients with microvascular

invasion: a Propensity Score Matching Cohort Study. Gastroenterol Res Pract. 2020;2020:4691425.
28. Ha SY, Sohn I, Hwang SH, Yang JW, Park CK. The prognosis of hepatocellular carcinoma after curative hepatectomy in young patients. Oncotarget. 2015;6(21):18664–73.
29. Su CW, Lei HJ, Chau GY, Hung HH, Wu JC, Hsia CY, et al. The effect of age on the long-term prognosis of patients with hepatocellular carcinoma after resection surgery: a propensity score matching analysis. Arch Surg. 2012;147(2):137–44.
30. Huang Z-Y, Liang B-Y, Xiong M, Zhan D-Q, Wei S, Wang G-P, et al. Long-term outcomes of repeat hepatic resection in patients with recurrent hepatocellular carcinoma and analysis of recurrent types and their prognosis: a single-center experience in China. Ann Surg Oncol. 2012;19(8):2515–25.

**How to cite this article:** Matsumoto M, Yanaga K, Shiba H, et al. Treatment of intrahepatic recurrence after hepatectomy for hepatocellular carcinoma. *Ann Gastroenterol Surg*. 2021;5:538–552. https://doi.org/10.1002/ags3.12449