Original article

# Long-term prognostic factors of patients with hepatocellular carcinoma who survive over ten years after hepatectomy.

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Short title

Long-term favorable factors of HCC

Authorship

SS and TK conceived the study concept and design, were involved with patient care and drafted the manuscript and literature review. TO, AN, YA, YS, HK, and AT were involved with the formation of the study concept and design, patient care and drafting of the manuscript and literature review.

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Competing interests

The authors declare no competing interests in relation to this study.

Synopsis

Important factors for long-term prognoses in HCC patients were solitary tumor, small tumors, and no advanced fibrosis. Even patients who relapse might survive long term if they have late or solitary intrahepatic recurrence, nonsevere cirrhosis, and curative treatment at recurrence.

## Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author.

The data are not publicly available due to privacy or ethical restrictions.

# Abstract

**Background and objectives:** The aim was to evaluate long-term prognostic factors in hepatocellular carcinoma (HCC) patients who survived over ten years after hepatectomy and compare prognostic factors between patients with recurrence who died and survived 10 years after initial hepatectomy.

**Methods:** We analyzed the HCC patients without recurrence over 10 years after hepatectomy (n=35), those with recurrence who survived over 10 years (n=48), and those who died within 10 years (n=132).

**Results:** The rate of recurrence was 16.3 %, ten-year overall survival (OS) rate was 38.6 %, and the ten-year recurrence-free survival (RFS) rate was 16.7 %. Nonviral, solitary tumor, well differentiation, and without severe fibrosis were independent favorable factors for long-term RFS. High cholinesterase levels, small tumor and without portal vein invasion were independent favorable factors for long-term survival among patients with recurrence. Long-term survivors with recurrence showed significantly low early recurrence, extrahepatic recurrence, multiple intrahepatic recurrence.

**Conclusion:** Important factors for long-term prognoses in HCC patients were solitary tumor, small tumors, and no advanced fibrosis. A treatment for nonviral hepatitis is needed to achieve long-term RFS. Even patients who relapse might survive long term if they have late or solitary intrahepatic recurrence, nonsevere cirrhosis, and curative treatment at recurrence.


**Keywords:** long-term prognoses; hepatectomy; hepatocellular carcinoma; nonviral hepatitis; solitary intrahepatic recurrence

# Text

## INTRODUCTION

It is estimated that 18.1 million new cancer cases and 9.6 million cancer-related deaths occurred in 2018 around the world [1]. Liver cancer is the seventh most frequent cancer, with an estimated 841,080 cases per year, and the second leading cause of cancer-related death; liver cancer is responsible for approximately 781,631 deaths per year [1]. Hepatocellular carcinoma (HCC) shows high recurrence rates, ranging from 70-75 % within five years after hepatectomy [2, 3]. Thus, these patients have many opportunities for the treatment of recurrence. According to the report of the Liver Cancer Study Group of Japan, the 3-year, 5-year, and 10-year overall survival (OS) rates of patients with HCC who undergo hepatectomy are 72.3 %, 56.8 % and 32.0 %, respectively [4]. Survival rates decrease over time. Several prognostic factors for the survival and recurrence of patients with resected HCC have been reported and include tumor size, tumor number, tumor marker, vascular invasion, and liver function [5-7]. However, reports on the prognostic factors of long-term survivors with resected HCC are rare. Therefore, in this study, we evaluated long-term prognostic factors in patients with HCC who survived over ten years after hepatectomy. We also compared prognostic factors between patients who died and survived 10 years after initial hepatectomy among those with recurrence.

## METHODS

### Patients and methods

Between January 2000 and November 2007, 339 consecutive patients with HCC underwent primary hepatectomy at the Gastroenterological Surgery I Unit of the Hokkaido University Hospital in Sapporo, Japan. We investigated 215 patients with confirmed outcomes ten years after hepatectomy, excluding deaths caused by other diseases. The hepatitis B virus (HBV) group included patients with HBV infection alone, the hepatitis C virus (HCV) group included patients with HCV infection alone, and the non-B non-C (NBNC) group included patients without HBV and HCV infection.

We divided the patients into three groups as follows: patients without recurrence over 10 years after hepatectomy (recurrence free: Group RF; n=35, 35/215, 16.3 %), patients with recurrence who survived over 10 years after hepatectomy (recurrence survive: Group RS; n=48, 48/215, 22.3 %), and patients who died within 10 years after hepatectomy excluding death caused by other diseases (recurrence dead: Group RD; n=132, 132/215, 61.4 %). First, we evaluated long-term survival and recurrence factors at primary hepatectomy and prognostic factors for survival among patients with recurrence. Second, we evaluated the timing of recurrence and treatment after recurrence.

This study was approved by the Hokkaido University Hospital Voluntary Clinical Study Committee (approval 018-0303) and was performed in accordance with the Helsinki Declaration guidelines.

**Hepatectomy**

The type of surgical procedure was usually determined based on the patients' liver function

reserve, i.e., according to the results of the indocyanine green retention test at 15 min (ICGR15) [8]. In principle, anatomical resection was performed for patients with an ICGR15 result less than 25 %. All surgeries showed that the surgical margins were histologically or macroscopically free. Fibrosis was defined as f3, bridging fibrosis or f4; cirrhosis was defined according to the general rules for the clinical and pathological study of primary liver cancer set by the Liver Cancer Study Group of Japan [4]. Postoperative morbidity was assessed using the validated Clavien–Dindo classification system [9]. Serious complications were categorized as grades III–V and defined as morbidity requiring surgical or radiological intervention.

**Follow-up after hepatectomy**

Follow-up studies after liver resection were conducted at 3-month intervals and included physical, serological (liver function, serum alpha-fetoprotein [AFP], and serum protein induced by vitamin K absence-II [PIVKA-II] tests), and radiological examinations (ultrasound sonography [US] and contrast-enhanced computed tomography [CT] scans or contrast-enhanced magnetic resonance imaging [MRI]).

**Statistical analyses**

Univariate analyses were performed using the chi-square test for noncontinuous variables. Logistic regression model analyses were performed for multivariate analyses. OS and recurrence-free survival (RFS) were analyzed by using the Kaplan-Meier method with the log-rank test or the Cox proportional hazards model. JMP Pro 14.0.0 for Windows (SAS Institute, Cary, NC) was used for the statistical analyses.

## RESULTS

### Prognoses of the study cohort

In this cohort of 215 study patients, the median survival time (MST) and ten-year OS rate were 69 months and 38.6 %, respectively. The ten-year RFS rate was 16.7 % (Figure 1).

### Long-term prognostic factors for recurrence

Table 1a presents the clinicopathological factors related to long-term RFS between Groups RF and RS+RD. The univariate analysis showed a significantly higher proportion of females, not NBNC, platelets ≥ 80,000/mm³, albumin (Alb) ≥ 4.0 g/dl, total bilirubin (T-bil) < 1.0 mg/dl, ICGR15 < 15 %, AFP < 20 ng/ml, tumor size < 4.5 cm, solitary tumor, well differentiation, patients without portal vein invasion (PVI), without f3/f4, anatomical resection, and blood loss at surgery < 200 ml in Group RF than in Group RS+RD.

The multivariate analysis indicated that not NBNC, solitary tumor, well differentiation, and without f3/f4 were independent favorable factors for long-term RFS (Table 1b).

### Long-term prognostic factors for survival

Table 2a presents the clinicopathological factors related to long-term OS between Groups RF+RS and RD. The univariate analysis showed a significantly higher proportion of age ≥ 60 years, Alb ≥ 4.0 g/dl, cholinesterase (ChE) ≥ 200 IU/L, ICGR15 < 15 %, AFP < 20 ng/ml, PIVKA-II < 100 mAU/ml, tumor size < 4.5 cm, solitary tumor, well differentiation, without PVI and hepatic vein invasion (HVI), without f3/f4, and blood loss at surgery < 200 ml in Group RF+RS than in Group RD.

The multivariate analysis indicated that AFP < 20 ng/ml, tumor size < 4.5 cm, solitary tumor, well differentiation, and without f3/f4 were independent favorable factors for long-term OS (Table 2b).

**Long-term prognostic factors for survival among patients with recurrence**

Table 3a presents the clinicopathological factors related to survival between Groups RS and RD. The univariate analysis showed a significantly higher proportion of age ≥ 60 years, Alb ≥ 4.0 g/dl, ChE ≥ 200 IU/L, AFP < 20 ng/ml, PIVKA-II < 100 mAU/ml, tumor size < 4.5 cm, solitary tumor, well differentiation, without PVI and HVI, without f3/f4, and blood loss at surgery < 200 ml in Group RS than in Group RD.

The multivariate analysis indicated that ChE ≥ 200 IU/L, tumor size < 4.5 cm, and without PVI were independent favorable factors for survival among patients with recurrence (Table 3b).

**Timing of recurrence, recurrence site and number, and treatment after recurrence**

Regarding the timing of recurrence, the rates of recurrence within 2 years and 6 months after hepatectomy in Group RS were 42 % and 6 %, respectively; those in Group RD were 85 % and 36 %, respectively. The median recurrence time after hepatectomy in Groups RS and RD was 32 (2-115) months and 8 (0.4-68) months, respectively ($p$<0.01). Group RD had significantly earlier recurrence (Figure 2).

Regarding the initial recurrence sites, extrahepatic recurrence was significantly higher in Group RD than in Group RS (65.2 % vs. 18.7 %) ($p$<0.01) (Table 4). In addition, multiple recurrence was a significantly unfavorable factor among patients with liver recurrence alone. Table 4 also shows the treatment methods after recurrence. Rehepatectomy, liver transplantation or ablation was

performed more often in Group RS than in Group RD. Moreover, the number of patients treated with systemic chemotherapy, including molecular target drugs or radiotherapy, was significantly lower in Group RS than in Group RD.

## DISCUSSION

The present study indicated that not NBNC, solitary tumor, well differentiation, and no underlying high-grade liver fibrosis were important factors for long-term survival and no recurrence over ten years. The group of patients who died within ten years after hepatectomy had significantly more individuals with early and extrahepatic recurrence than those who survived with recurrence. Multiple recurrence was a significantly unfavorable factor among patients with liver recurrence alone. The patients who survived with recurrence more frequently underwent hepatectomy, liver transplantation or ablation than patients who died within ten years.

Few previous studies have focused on the prognoses of long-term survivors with HCC for more than 10 years worldwide [10-22]. This study showed that the ten-year OS rate was 38.6 %, which is consistent with previous reports, with OS rates ranging from 21.8-32.0 % [4,15,16,19,22]. The rate of no recurrence was 16.3 %, and the rate of recurrence within ten years after hepatectomy was 83.7 %. These results are also consistent with those of other reports, with rates ranging from 8.7-30.6 % [15,19,22]. Eguchi et al. reported that the ten-year RFS rate after hepatectomy for HCC was 22.4 % and that solitary tumor, tumor size less than 5 cm, simple nodular type, and low tumor markers were favorable factors for long-term RFS [18]. Kim et al. reported that the ten-year RFS rate

after hepatectomy for HCC was 24.1 % and that HBe-Ag positivity, satellite nodules, vascular invasion, and high ICGR15 values were unfavorable factors for long-term RFS [19]. Another report showed that ten-year RFS rates after hepatectomy for HCC were 9.9-11.7 % [11,16]. In 2005, Shimada et al. reported that HCV-Ab positivity was an unfavorable factor for long-term RFS [15]. In contrast, NBNC was an unfavorable factor for long-term RFS in this study. This discrepancy might be explained by the following: in recent years, HCV gas been controlled with antiviral drugs, and it was reported that the sustained virologic response (SVR) rate was 95.2 % with HCV, 95.9 % with Child-Pugh class A and 88.3 % with Child-Pugh class B [23]. However, no treatment has been established for NBNC. Several studies have claimed that underlying liver fibrosis and cirrhosis might predispose patients to multicentric hepatocarcinogenesis [24,25], and the risk of HCC was 24 times higher in patients with severe cirrhosis than in patients with normal or mild fibrosis [26]. Although no significance was observed in the multivariate analysis, female sex was significantly favorable for RFS in the univariate analysis. Some studies have reported that a potential role of androgen is associated with liver carcinogenesis [27, 28]. Regarding long-term RFS, tumor size was not an independent factor, but solitary tumor was a strongly favorable factor in the multivariate analysis. It has been reported that solitary large HCC has better molecular characteristics than nodular HCC; these characteristics are derived from differences in gene expression, e.g., cathepsin L, integrin alpha6, and RhoC [29].

On the other hand, our results showed that low AFP, small tumor size, solitary tumor, well differentiation, and without f3/f4 were independent favorable factors for long-term OS. These results

are consistent with those of previous reports [15,16,19,21,22]. Regarding long-term prognostic factors among patients with HCC who experienced recurrence within ten years after hepatectomy, small tumor size, high ChE and without PVI were independent favorable factors for long-term survival. The patients who survived more than ten years after hepatectomy showed significantly less early recurrence and less extrahepatic recurrence. Large HCC is a risk factor for PVI [30]. PVI is also known as a risk factor for the early recurrence of HCC [31].

Serum ChE is known as a biomarker of liver cirrhosis [32]. No underlying severe liver cirrhosis is very important for the treatment of secondary liver recurrence to achieve curative treatment. Because improved liver function, i.e., ChE, was one of the favorable prognostic factors for HCC [33] and, in this study, the absence of high-grade liver fibrosis was an important factor for long-term survival and no recurrence over ten years, the improvement in fibrosis for the treatment of viral hepatitis and nonalcoholic steatohepatitis (NASH) was necessary for long-term survival regardless of recurrence.

In this study, early recurrence is a strong unfavorable factor. Zheng et al. reported that 6 % of long-term survivors experienced recurrence within 2 years, while 77 % of short-term survivors experienced recurrence [22]. Poon et al. reported that early recurrence (within 1 year) arises mainly from intrahepatic metastases, which tend to be multifocal, and that late recurrence (after 1 year) is more likely to be related to multicentric occurrence in origin [34]. Consistent with these results, intrahepatic recurrence in non-long-term survivors might originate from not only multicentric occurrence but also intrahepatic secondary metastases. This study showed that multiple recurrence

was a significantly unfavorable factor among patients with liver recurrence alone. Multiple intrahepatic recurrence is associated with intrahepatic metastases [35].

Radical treatments, such as rehepatectomy, liver transplantation or ablation, are often performed in long-term survivors [20,21]. Minagawa et al. reported that repeat hepatic resection was very useful for improving prognoses, especially in patients with single HCC at primary resection, negative portal invasion at repeat resection, and a disease-free interval of more than 1 year after initial hepatectomy [36]. Belghiti et al. reported the usefulness of salvage liver transplantation, and the results of salvage liver transplantation were almost the same as those of first liver transplantation [37]. In addition, it was reported that though hepatic resection was the most effective treatment for recurrent HCC, ablation could be a safe and effective option for the majority of patients with recurrence who were unsuitable for surgery in a systematic review of 19 studies [38].

In this study, the long-term survival of patients with extrahepatic recurrence was insufficient. However, Nakagawa et al. reported that patients who had a disease-free interval of more than 1 year and AFP $\geq$ 500 ng/ml after pulmonary metastasectomy of HCC showed 3- and 5-year survival rates of 89 % and 74 %, respectively [39]. Thus, we might try aggressive surgical management for suitable patients.

## Conclusions

The important factors for long-term prognoses of more than ten years in patients with HCC were solitary tumor, small tumors, and no advanced fibrosis. In addition, the development of a

treatment for nonviral hepatitis is needed to achieve long-term RFS. Even patients who experience relapse might be long-term survivors if they have late or solitary intrahepatic recurrence, nonsevere cirrhosis, and curative treatment at recurrence.

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## Abbreviations list

HCC: Hepatocellular carcinoma; HBs-Ag: HBs-antigen; HCV-Ab: HCV-antibody; ICGR15: indocyanine green retention test at 15 min; AFP: Alpha-fetoprotein; PIVKA-II: Protein induced by vitamin K absence-II; US: Ultrasound sonography; CT: Computed tomography; MRI: Magnetic resonance imaging; OS: Overall survival; RFS: Relapse-free survival; MST: Median survival time; NBNC: non-B non-C; PVI: Portal vein invasion; TACE: Transarterial chemoembolization; PT: Prothrombin time; HVI: Hepatic vein invasion; ChE: Cholinesterase.

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# Figure legends

**Fig. 1**

Overall survival (OS) and Relapse-free survival (RFS) of this cohort.

**Fig. 2**

Recurrence rates and time after hepatectomy in the RS and RD groups.

**Table 1. Clinicopathological characteristics of RF and RS+RD**

(a) Clinicopathological characteristics by univariate analyses

| Characteristics | | RF (n = 35) | RS+RD (n = 180) | *p* |
|---|---|---|---|---|
| **Epidemiology** | | | | |
| Age | < 60 | 16 (46 %) | 86 (48 %) | *0.82* |
| | ≥ 60 | 19 (54 %) | 94 (52 %) | |
| Sex | male | 25 (71 %) | 154 (86 %) | *0.04* |
| | Female | 10 (29 %) | 26 (14 %) | |
| HBs-Ag | positive | 20 (57 %) | 84 (47 %) | *0.25* |
| | negative | 15 (43 %) | 96 (53 %) | |
| HCV-Ab | positive | 12 (34 %) | 48 (27 %) | *0.35* |
| | negative | 23 (66 %) | 132 (73 %) | |
| NBNC | yes | 3 (9 %) | 48 (27 %) | *0.02* |
| | No | 32 (91 %) | 132 (73 %) | |
| **Biochemical Factors** | | | | |
| Platelets | < 80,000 /mm³ | 0 (0 %) | 19 (11 %) | *0.04* |
| | ≥ 80,000 /mm³ | 35 (100 %) | 161 (89 %) | |
| Albumin | < 4.0 g/dl | 8 (23 %) | 77 (43 %) | *0.02* |
| | ≥ 4.0 g/dl | 27 (77 %) | 103 (57 %) | |
| Total bilirubin | ≥ 1.0 mg/dl | 3 (9 %) | 48 (27 %) | *0.02* |
| | < 1.0 mg/dl | 32 (91 %) | 132 (73 %) | |
| PT | < 80 % | 5 (14 %) | 48 (27 %) | *0.11* |
| | ≥ 80 % | 30 (86 %) | 132 (73 %) | |
| ChE | < 200 IU/L | 7 (20 %) | 62 (34 %) | *0.09* |
| | ≥ 200 IU/L | 28 (80 %) | 118 (66 %) | |
| ICGR15 | ≥ 15 % | 8 (23 %) | 91 (51 %) | *<0.01* |
| | < 15 % | 27 (77 %) | 89 (49 %) | |
| AFP | ≥ 20 ng/ml | 13 (37 %) | 101 (56 %) | *0.03* |
| | < 20 ng/ml | 22 (63 %) | 79 (44 %) | |
| PIVKA-II | ≥ 100 mAU/ml | 17 (49 %) | 105 (58 %) | *0.28* |
| | < 100 mAU/ml | 18 (51 %) | 75 (42 %) | |
| **Tumor Factors** | | | | |
| Tumor size | ≥ 4.5 cm | 13 (37 %) | 100 (56 %) | *0.04* |
| | < 4.5 cm | 22 (63 %) | 80 (44 %) | |

| | | | | |
|---|---|---|---|---|
| Tumor number | multiple | 4 (11 %) | 82 (46 %) | *<0.01* |
| | solitary | 31 (89 %) | 98 (54 %) | |
| Macroscopic type | simple nodular | 20 (57 %) | 87 (48 %) | *0.34* |
| | others | 15 (43 %) | 93 (52 %) | |
| Differentiation | well | 5 (14 %) | 9 (5 %) | *0.04* |
| | others | 30 (86 %) | 171 (95 %) | |
| PVI | yes | 5 (14 %) | 56 (31 %) | *0.04* |
| | no | 30 (86 %) | 124 (69 %) | |
| HVI | yes | 1 (3 %) | 22 (12 %) | *0.10* |
| | no | 34 (97 %) | 158 (88 %) | |
| **Underlying Liver** | | | | |
| Fibrosis | f3/4 | 9 (26 %) | 107 (59 %) | *<0.01* |
| | f0-2 | 26 (74 %) | 73 (41 %) | |
| **Surgical Factors** | | | | |
| Anatomical resection | yes | 31 (89 %) | 131 (73 %) | *0.04* |
| | no | 4 (11 %) | 49 (27 %) | |
| Operative time | ≥ 180 min | 32 (91 %) | 173 (96 %) | *0.22* |
| | < 180 min | 3 (9 %) | 7 (4 %) | |
| Blood loss | ≥ 200 ml | 21 (60 %) | 139 (77 %) | *0.03* |
| | < 200 ml | 14 (40 %) | 41 (23 %) | |

RF, Recurrence-free group; RS, Recurrence-survival group; RD, Recurrence-death group; HBs-Ag, HBs-antigen; HCV-Ab, HCV-antibody; NBNC, without HBV and HCV; PT, prothrombin time; ChE, cholinesterase; ICGR15, indocyanine green retention rate at 15 min; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; PVI, portal venous invasion; HVI, hepatic venous invasion; f3, bridging fibrosis; f4, cirrhosis.

**Table 1. Clinicopathological characteristics of RF and RS+RD**

(b) Clinicopathological characteristics by multivariate analyses

| Characteristics | Odds ratio | 95% CI | *P* |
|---|---|---|---|
| Sex Female | 2.3688 | 0.6920-8.1081 | *0.16* |
| Not NBNC | 5.8812 | 1.6237-21.3019 | *<0.01* |
| Platelets ≥ 80,000 /mm³ | 2.0707 | 0.1204-35.6142 | *0.61* |
| Albumin ≥ 4.0 g/dl | 1.7456 | 0.5993-5.0845 | *0.30* |
| Total bilirubin < 1.0 mg/dl | 3.6286 | 0.7536-17.4732 | *0.10* |
| ICGR15 < 15 % | 2.0019 | 0.6500-6.1657 | *0.22* |
| AFP < 20 ng/ml | 1.7616 | 0.6688-4.6403 | *0.25* |
| Tumor size < 4.5 cm | 1.0021 | 0.3457-2.9047 | *0.99* |
| Solitary tumor | 11.7775 | 2.6214-52.9132 | *<0.01* |
| Well differentiation | 18.6768 | 2.7686-125.9936 | *<0.01* |
| PVI negative | 1.4960 | 0.4180-5.3539 | *0.53* |
| Fibrosis f3/4 negative | 7.8509 | 2.7037-22.7969 | *<0.01* |
| Anatomical resection | 2.1250 | 0.4769-9.4690 | *0.32* |
| Blood loss < 200 ml | 1.6918 | 0.5858-4.8863 | *0.33* |

NBNC, without HBV and HCV; ICGR15, indocyanine green retention rate at 15 min; AFP, alpha-fetoprotein; PVI, portal venous invasion; f3, bridging fibrosis; f4, cirrhosis.

**Table 2. Clinicopathological characteristics of RF+RS and RD**

(a) Clinicopathological characteristics by univariate analyses

| Characteristics | | RF+RS (n = 83) | RD (n = 132) | *p* |
|---|---|---|---|---|
| **Epidemiology** | | | | |
| Age | < 60 | 31 (37 %) | 71 (54 %) | *0.01* |
| | ≥ 60 | 52 (63 %) | 61 (46 %) | |
| Sex | male | 65 (78 %) | 114 (86 %) | *0.12* |
| | Female | 18 (22 %) | 18 (14 %) | |
| HBs-Ag | positive | 46 (55 %) | 58 (44 %) | *0.10* |
| | negative | 37 (45 %) | 74 (56 %) | |
| HCV-Ab | positive | 22 (27 %) | 38 (29 %) | *0.71* |
| | negative | 61 (73 %) | 94 (71 %) | |
| NBNC | yes | 15 (18 %) | 36 (27 %) | *0.12* |
| | No | 68 (82 %) | 96 (73 %) | |
| **Biochemical Factors** | | | | |
| Platelets | < 80,000 /mm³ | 4 (5 %) | 13 (10 %) | *0.18* |
| | ≥ 80,000 /mm³ | 79 (95 %) | 119 (90 %) | |
| Albumin | < 4.0 g/dl | 22 (27 %) | 63 (48 %) | *<0.01* |
| | ≥ 4.0 g/dl | 61 (73 %) | 69 (52 %) | |
| Total bilirubin | ≥ 1.0 mg/dl | 15 (18 %) | 36 (27 %) | *0.12* |
| | < 1.0 mg/dl | 68 (82 %) | 96 (73 %) | |
| PT | < 80 % | 19 (23 %) | 34 (26 %) | *0.63* |
| | ≥ 80 % | 64 (77 %) | 98 (74 %) | |
| ChE | < 200 IU/L | 17 (20 %) | 52 (39 %) | *<0.01* |
| | ≥ 200 IU/L | 66 (80 %) | 80 (61 %) | |
| ICGR15 | ≥ 15 % | 30 (36 %) | 69 (52 %) | *0.02* |
| | < 15 % | 53 (64 %) | 63 (48 %) | |
| AFP | ≥ 20 ng/ml | 32 (39 %) | 78 (59 %) | *<0.01* |
| | < 20 ng/ml | 51 (61 %) | 54 (41 %) | |
| PIVKA-II | ≥ 100 mAU/ml | 38 (46 %) | 84 (64 %) | *0.01* |
| | < 100 mAU/ml | 45 (54 %) | 48 (36 %) | |
| **Tumor Factors** | | | | |
| Tumor size | ≥ 4.5 cm | 25 (30 %) | 86 (65 %) | *<0.01* |
| | < 4.5 cm | 58 (70 %) | 46 (35 %) | |

| | | | | |
|---|---|---|---|---|
| Tumor number | multiple | 19 (23 %) | 67 (51 %) | *<0.01* |
| | solitary | 64 (77 %) | 65 (59 %) | |
| Macroscopic type | simple nodular | 47 (57 %) | 60 (45 %) | *0.11* |
| | others | 36 (43 %) | 72 (55 %) | |
| Differentiation | well | 10 (12 %) | 4 (3 %) | *<0.01* |
| | others | 73 (88 %) | 128 (97 %) | |
| PVI | yes | 12 (14 %) | 49 (37 %) | *<0.01* |
| | no | 71 (86 %) | 83 (63 %) | |
| HVI | yes | 3 (4 %) | 20 (15 %) | *<0.01* |
| | no | 80 (96 %) | 112 (85 %) | |
| **Underlying Liver** | | | | |
| Fibrosis | f3/4 | 36 (43 %) | 79 (60 %) | *0.01* |
| | f0-2 | 47 (57 %) | 53 (40 %) | |
| **Surgical Factors** | | | | |
| Anatomical resection | yes | 68 (82 %) | 94 (71 %) | *0.07* |
| | no | 15 (18 %) | 38 (29 %) | |
| Operative time | ≥ 180 min | 78 (94 %) | 127 (96 %) | *0.44* |
| | < 180 min | 5 (6 %) | 5 (4 %) | |
| Blood loss | ≥ 200 ml | 52 (63 %) | 108 (82 %) | *<0.01* |
| | < 200 ml | 31 (37 %) | 24 (18 %) | |

RF, Recurrence-free group; RS, Recurrence-survival group; RD, Recurrence-death group; HBs-Ag, HBs-antigen; HCV-Ab, HCV-antibody; NBNC, without HBV and HCV; PT, prothrombin time; ChE, cholinesterase; ICGR15, indocyanine green retention rate at 15 min; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; PVI, portal venous invasion; HVI, hepatic venous invasion; f3, bridging fibrosis; f4, cirrhosis.

**Table 2. Clinicopathological characteristics of RF+RS and RD**

(b) Clinicopathological characteristics by multivariate analyses

| Characteristics | Odds ratio | 95% CI | *p* |
|---|---|---|---|
| Age ≥ 60 | 0.5016 | 0.2453-1.0255 | *0.05* |
| ChE ≥ 200 IU/L | 1.2705 | 0.5748-2.8083 | *0.55* |
| Albumin ≥ 4.0 g/dl | 1.1253 | 0.5261-2.4071 | *0.76* |
| ICGR15 < 15 % | 1.6285 | 0.7970-3.3276 | *0.18* |
| AFP < 20 ng/ml | 2.0013 | 1.0142-3.9493 | *0.04* |
| PIVKA-II < 100 mAU/ml | 0.8602 | 0.3933-1.8813 | *0.70* |
| Tumor size < 4.5 cm | 4.1825 | 1.8065-9.6837 | *<0.01* |
| Solitary tumor | 2.6579 | 1.2656-5.5820 | *<0.01* |
| Well differentiation | 4.7835 | 1.0637-21.5107 | *0.04* |
| PVI negative | 1.3650 | 0.5722-3.2562 | *0.48* |
| HVI negative | 2.3858 | 0.5700-9.9853 | *0.23* |
| Fibrosis f3/f4 | 3.5454 | 1.5677-8.0179 | *<0.01* |
| Blood loss < 200 ml | 1.6677 | 0.7614-3.6526 | *0.20* |

ChE, cholinesterase; Alb, albumin; ICGR15, indocyanine green retention rate at 15 min; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; PVI, portal venous invasion; HVI, hepatic venous invasion; f3, bridging fibrosis; f4, cirrhosis.

**Table 3. Clinicopathological characteristics of RS and RD**

(a) Clinicopathological characteristics by univariate analyses

| Characteristics | | RS (n = 48) | RD (n = 132) | *p* |
|---|---|---|---|---|
| **Epidemiology** | | | | |
| Age | < 60 | 15 (31 %) | 71 (54 %) | *<0.01* |
| | ≥ 60 | 33 (69 %) | 61 (46 %) | |
| Sex | male | 40 (83 %) | 114 (86 %) | *0.60* |
| | female | 8 (17 %) | 18 (14 %) | |
| HBs-Ag | positive | 26 (54 %) | 58 (44 %) | *0.22* |
| | negative | 22 (46 %) | 74 (56 %) | |
| HCV-Ab | positive | 10 (21 %) | 38 (29 %) | *0.28* |
| | negative | 38 (79 %) | 94 (71 %) | |
| NBNC | yes | 12 (25 %) | 36 (27 %) | *0.76* |
| | No | 36 (75 %) | 96 (73 %) | |
| **Biochemical Factors** | | | | |
| Platelets | < 80,000 /mm³ | 4 (8 %) | 13 (10 %) | *0.75* |
| | ≥ 80,000 /mm³ | 44 (92 %) | 119 (90 %) | |
| Albumin | < 4.0 g/dl | 14 (29 %) | 63 (48 %) | *0.02* |
| | ≥ 4.0 g/dl | 34 (71 %) | 69 (52 %) | |
| Total bilirubin | ≥ 1.0 mg/dl | 12 (25 %) | 36 (27 %) | *0.76* |
| | < 1.0 mg/dl | 36 (75 %) | 96 (73 %) | |
| PT | < 80 % | 14 (29 %) | 34 (26 %) | *0.64* |
| | ≥ 80 % | 34 (71 %) | 98 (74 %) | |
| ChE | < 200 IU/L | 10 (21 %) | 52 (39 %) | *0.02* |
| | ≥ 200 IU/L | 38 (79 %) | 80 (61 %) | |
| ICGR15 | ≥ 15 % | 22 (46 %) | 69 (52 %) | *0.44* |
| | < 15 % | 26 (54 %) | 63 (48 %) | |
| AFP | ≥ 20 ng/ml | 19 (40 %) | 78 (59 %) | *0.02* |
| | < 20 ng/ml | 29 (60 %) | 54 (41 %) | |
| PIVKA-II | ≥ 100 mAU/ml | 21 (44 %) | 84 (64 %) | *0.01* |
| | < 100 mAU/ml | 27 (56 %) | 48 (36 %) | |
| **Tumor Factors** | | | | |
| Tumor size | ≥ 4.5 cm | 12 (25 %) | 86 (65 %) | *<0.01* |
| | < 4.5 cm | 36 (75 %) | 46 (35 %) | |

| | | | | |
|---|---|---|---|---|
| Tumor number | multiple | 15 (31 %) | 67 (51 %) | *0.02* |
| | solitary | 33 (69 %) | 65 (49 %) | |
| Macroscopic type | simple nodular | 27 (56 %) | 60 (45 %) | *0.20* |
| | others | 21 (44 %) | 72 (55 %) | |
| Differentiation | well | 5 (10 %) | 4 (3 %) | *0.04* |
| | others | 43 (90 %) | 12 (97 %) | |
| PVI | yes | 7 (15 %) | 49 (37 %) | *<0.01* |
| | no | 41 (85 %) | 83 (63 %) | |
| HVI | yes | 2 (4 %) | 20 (15 %) | *0.04* |
| | no | 46 (96 %) | 112 (85 %) | |
| **Underlying Liver** | | | | |
| Fibrosis | f3/4 | 28 (58 %) | 79 (60 %) | *0.85* |
| | f0-2 | 20 (42 %) | 53 (40 %) | |
| **Surgical Factors** | | | | |
| Anatomical resection | yes | 37 (77 %) | 94 (71 %) | *0.43* |
| | no | 11 (23 %) | 38 (29 %) | |
| Operative time | ≥ 180 min | 46 (96 %) | 127 (96 %) | *0.90* |
| | < 180 min | 2 (4 %) | 5 (4 %) | |
| Blood loss | ≥ 200 ml | 31 (65 %) | 108 (82 %) | *0.01* |
| | < 200 ml | 17 (35 %) | 24 (18 %) | |

RS, Recurrence-survival group; RD, Recurrence-death group; HBs-Ag, HBs-antigen; HCV-Ab, HCV-antibody; NBNC, without HBV and HCV; PT, prothrombin time; ChE, cholinesterase; ICGR15, indocyanine green retention rate at 15 min; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; PVI, portal venous invasion; HVI, hepatic venous invasion; f3, bridging fibrosis; f4, cirrhosis.

**Table 3. Clinicopathological characteristics of RS and RD**

(b) Clinicopathological characteristics by multivariate analyses

| Characteristics | Odds ratio | 95% CI | *p* |
|---|---|---|---|
| Age ≥ 60 | 0.5548 | 0.2555-1.2046 | *0.13* |
| ChE ≥ 200 IU/L | 3.3088 | 1.3460-8.1335 | *<0.01* |
| Albumin ≥ 4.0 g/dl | 1.1073 | 0.4585-2.6743 | *0.82* |
| AFP < 20 ng/ml | 2.0606 | 0.9039-4.6972 | *0.08* |
| PIVKA-II < 100 mAU/ml | 0.7171 | 0.2841-1.8103 | *0.48* |
| Tumor size < 4.5 cm | 3.1530 | 1.2952-7.6754 | *0.01* |
| Solitary tumor | 1.7216 | 0.7371-4.0207 | *0.20* |
| Well differentiation | 3.0987 | 0.5785-16.5992 | *0.18* |
| PVI negative | 3.6316 | 1.0789-12.2237 | *0.03* |
| HVI negative | 1.8456 | 0.3314-10.2790 | *0.48* |
| Blood loss < 200 ml | 1.4836 | 0.6035-3.6473 | *0.39* |

ChE, cholinesterase; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence-II; PVI, portal venous invasion; HVI, hepatic venous invasion.

**Table 4. Initial recurrence patterns and treatment after recurrence**

| | RS (n = 48) | RD (n = 132) | *p* |
|---|---|---|---|
| **Recurrence site** | | | |
| Liver only | 39 (81 %) | 46 (35 %) | *<0.01* |
| Extrahepatic | 9 (19 %) | 86 (65 %) | |
| **Tumor number of liver recurrence alone** | (n=39) | (n=46) | |
| Multiple | 9 (23 %) | 31 (67 %) | *<0.01* |
| **Treatment after recurrence** | | | |
| Re-hepatectomy | 23 (48 %) | 20 (15 %) | *<0.01* |
| Liver transplantation | 5 (10 %) | 3 (2 %) | *0.01* |
| Ablations | 29 (60 %) | 30 (23 %) | *<0.01* |
| TACE | 27 (56 %) | 88 (67 %) | *0.19* |
| Resection of metastases | 7 (15 %) | 23 (17 %) | *0.79* |
| Systemic chemotherapy including molecular target drug | 9 (19 %) | 56 (42 %) | *<0.01* |
| Radiotherapy | 1 (2 %) | 36 (27 %) | *<0.01* |

RS, Recurrence-survival group; RD, Recurrence-death group; TACE, transarterial chemoembolization.

Figure 1

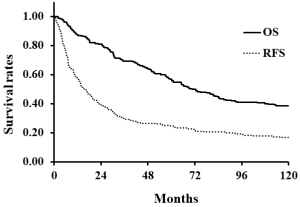
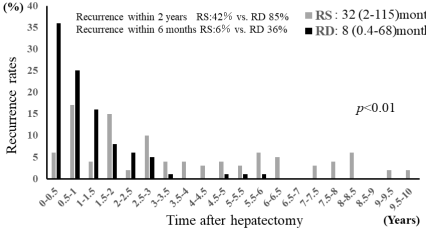

1.00
0.80
0.60
0.40
0.20
0.00
Survival rates
OS
RFS
0
24
48
72
96
120
Months

Figure 2


(%)
40
35
30
25
20
15
10
5
0
Recurrence rates
Recurrence within 2 years RS:42% vs. RD 85%
Recurrence within 6 months RS:6% vs. RD 36%
RS : 32 (2-115)months
RD: 8 (0.4-68)months
p<0.01
0-0.5
0.5-1
1-1.5
1.5-2
2-2.5
2.5-3
3-3.5
3.5-4
4-4.5
4.5-5
5-5.5
5.5-6
6-6.5
6.5-7
7-7.5
7.5-8
8-8.5
8.5-9
9-9.5
9.5-10
Time after hepatectomy
(Years)