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Prognostic significance of early and multiple recurrences after curative resection for hepatocellular carcinoma

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Abstract

Background In hepatocellular carcinoma (HCC), postoperative recurrence remains high. This study aimed to evaluate the recurrence patterns and prognosis of HCC after curative hepatectomy.

Methods Among 352 patients with primary HCC who underwent initial hepatectomy between January 2002 and December 2022, 151 with recurrence were assessed for the relationship between recurrence pattern and prognosis.

Results The early recurrence group (within 6 months postoperatively; $n=38$) had significantly higher serum alpha-fetoprotein ($p=0.002$), des-γ-carboxyprothrombin (DCP; $p=0.004$) levels and Barcelona Clinic Liver Cancer (BCLC) stage ($p<0.001$), larger tumor size ($p<0.001$), higher incidence of multiple tumors ($p=0.002$) and lower overall survival (OS) ($p<0.001$) than the late recurrence group (> 6 months postoperatively; $n=113$). The tumor size ($p=0.013$) and BCLC stage ($p=0.001$) were independent risk factors for early recurrence within 6 months in multivariate analysis.

The multiple recurrence group (intrahepatic multinodular recurrence or distant metastasis; $n=89$) had significantly lower prognostic nutritional index ($p=0.026$), larger tumor size ($p=0.017$), lower incidence of liver cirrhosis ($p=0.03$) than the single recurrence group (single nodule recurrence; $n=62$). The multiple recurrence group, especially patients with ≥ three intrahepatic nodules and distant metastases, had lower postoperative OS ($p<0.001$) and shorter time to recurrence ($p<0.001$) than the single recurrence group.

When the patients were classified into three groups: late recurrence with one or two tumors (Group A; $n=74$), early recurrence or three or more tumors or distant metastasis (Group B; $n=54$), and early recurrence with three or more tumors or distant metastasis (Group C; $n=23$), OS was significantly lower in Groups B and C than Group A ($p<0.001$).

Conclusions Patients with early recurrence within 6 months after surgery and three or more recurrence nodule or distant metastasis exhibited poor prognosis after initial recurrence, and they should be carefully followed up.

Keywords Hepatocellular carcinoma, Curative hepatectomy, Early recurrence, Multiple recurrence, Metachronous multicentric occurrence, Intrahepatic metastases

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Background

Among the various treatment options for hepatocellular carcinoma (HCC), liver resection and radiofrequency ablation (RFA) are the optimal modalities with curative intent for early-stage HCC. However, the incidence of HCC recurrence, mainly in the remnant liver, remains

high because the mechanisms underlying liver carcinogenesis are closely associated with the underlying chronic liver disease. HCC differs from other digestive cancers because it has a distinct etiology. Japanese guidelines [1] recommend that recurrent HCCs be treated in the same manner as the initial lesions. This concept is based on the metachronous multicentric occurrence (MO) theory, which states that recurrent HCC is independent of the primary HCC, and patients who underwent repeat hepatectomy for intrahepatic recurrence after curative resection demonstrated better survival than the non-surgery group [2]. However, unexpected early diffuse and multinodular recurrences may occur in the remnant liver after curative resection, resulting in poor prognosis. Such recurrence patterns may be due to intrahepatic metastases (IM) rather than MO. In such cases, repeat hepatectomy, RFA, or initial surgery with curative intent for IM may not provide a survival benefit. However, distinguishing between the two types of intrahepatic recurrence and predicting which type of recurrence will occur are challenging.

In the American Association for the Study of Liver Diseases and Japanese guidelines, hepatectomy is indicated for HCC limited to three nodules in the liver [1, 3]. However, several reports have shown the benefit of surgical treatment in selected cases of intermediate-stage HCC [4, 5]. Japanese guidelines expanded the surgical indication to advanced HCC with limited portal vein tumor thrombus (PVTT) [1]. However, to appropriately expand the indications for surgery and avoid unnecessary surgeries, predicting the risk of fulminant early and multiple recurrences is important.

The present study aimed to clarify the relationship between the recurrence patterns of HCC and the preoperative and postoperative characteristics of initial hepatectomy.

Methods

Participants

We reviewed the database of patients with primary HCC who underwent an initial hepatectomy at Mie University Hospital between January 2002 and December 2022 and identified 352 consecutive cases. The diagnosis of HCC was made radiologically preoperatively based on the findings of dynamic enhanced computed tomography (CT) and confirmed histologically in the resected specimens. During the follow-up after hepatectomy, 170 patients experienced recurrence. Among these, 16 who underwent non-curative reduction hepatectomy or had missing data were excluded from this study. Three patients with very early recurrence within two months were also excluded from this study, as such recurrences are primarily attributed to residual tumor. Finally, 151 patients were assessed to determine the relationship between recurrence type and patient background or prognosis. All experimental protocols were approved by the Medical Ethics Committee of the Mie University Hospital (H2021-156). This study was informed to all participants by opt-out on website of our institution with the opportunity to reject their enrollment to this study instead of obtaining written consent form from the participants because of observational study.

Preoperative laboratory data, including preoperative patient status, standard liver biochemistry, and tumor markers, including serum alpha-fetoprotein (AFP) and des-γ-carboxyprothrombin (DCP), were assessed. Indocyanine green retention (ICG) test and Technetium-99 m-diethylenetriaminepentaacetic acid-galactosyl-human serum albumin (GSA) liver scintigraphy were performed to assess the liver functional reserve. Data on maximum tumor diameter, tumor number, and Barcelona Clinic Liver Cancer (BCLC) stage were collected to assess tumor progression. Up-to-7 criteria [6] and 5–5-500 criteria [7], which are used in the field of liver transplantation for HCC, were also evaluated. For immuno-nutritional/inflammatory assessment, prognostic nutritional index (PNI) was calculated from serum albumin level and lymphocyte count, as previously described: $10 \times$albumin (g/dl) $+ 0.005 \times$total lymphocyte count (per mm^3) [8]. Perioperative surgical outcomes, including operative time, blood loss, and postoperative complications using Clavien-Dindo classification [9] were assessed, and postoperative laboratory data associated with liver function (total bilirubin and prothrombin time international normalized ratio [PT-INR]) on postoperative day (POD) 5 were also assessed. In addition, histological findings of the tumor and liver were assessed. Presence of micro- and macrovascular tumor thrombus was assessed according to Liver Cancer Study Group of Japan classification [10]. The treatments administered after recurrence were also evaluated.

The 151 patients with HCC recurrence after surgery were assessed for their initial recurrence patterns, focusing on the time to recurrence and the number of recurrent tumors. Early recurrence was defined as recurrence between 2–6 months postoperatively, and late recurrence was defined as recurrence more than 6 month after surgery. Based on these definitions, the patients were divided into two groups: early recurrence ($n=38$) and late recurrence ($n=113$) groups in Study 1 (Fig. 1). Furthermore, the patients were divided into two groups based on the number of initial recurrent tumors: single recurrence ($n=62$, having a single nodule in the liver) and multiple recurrence ($n=89$, having $\geq$ two nodules in the liver or distant metastasis) groups in Study 2 (Fig. 1).

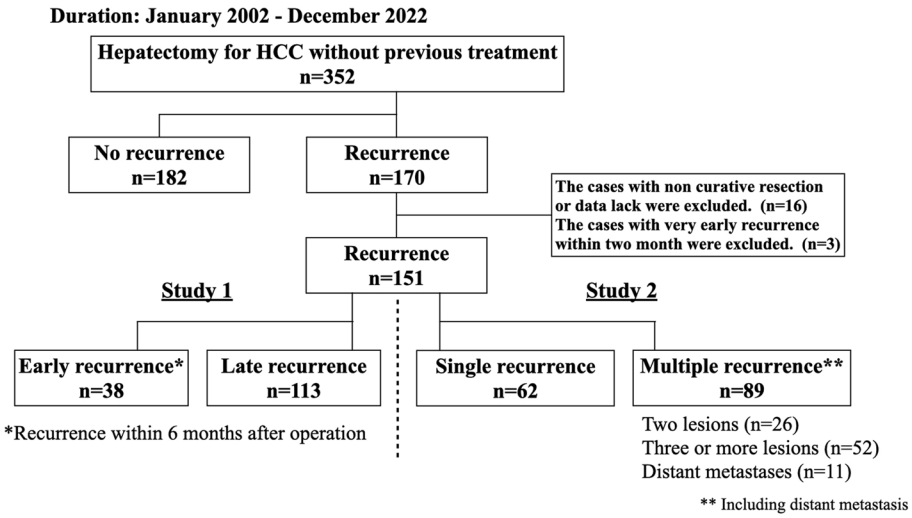

Fig. 1 Flow diagram of patients with HCC who underwent hepatectomy without previous treatment

Determination of the type of hepatectomy

After the diagnosis of HCC, the most appropriate surgical procedure was determined depending on the tumor size and location and liver functional reserve based on the findings of ICGR15 and the GSA uptake ratio of LHL15, as previously described [11, 12]. To summarize briefly, our surgical strategy is to achieve margin-negative liver resection. For cases with small tumors located in peripheral areas, partial liver resection is performed. For cases with relatively large tumors located in deep areas near Glisson's capsule or with multiple nodules in a unilateral lobe, anatomical resection is applied. We always ensure a plasma disappearance rate of ICG (KICG) greater than 0.05 in the future liver remnant, calculated from KICG × remnant liver volume rate [13], analyzed using CT volumetry or SYNAPSE VINCENT by Fujifilm. Liver parenchymal transection is performed using the cavitron ultrasonic suction aspirator (CUSA). The Pringle maneuver is employed during parenchymal transection when bleeding control is challenging, as determined by the surgeon. Laparoscopic liver resection has been applied for HCC since 2008, initially limited to peripheral small tumors and now extended to almost all procedures, except for large tumors of 10 cm or more or cases with severe adhesion.

Patient follow-up after hepatectomy

Postoperative follow-up consisted of periodic blood tests and monitoring of tumor markers (AFP and DCP levels). Dynamic CT and/or magnetic resonance imaging (MRI) of the remnant liver was performed every 3–4 months until 2 years after hepatectomy and every 6 months after that. Chest CT, whole abdominal CT, brain MRI, and bone scintigraphy were performed if a recurrence of extrahepatic HCC was suspected. The median follow-up period was 34 (1–217) months. All patients in the late recurrence group were followed up for > 6 months.

Treatment strategy after recurrence

When recurrence was found after hepatectomy, patients were treated according to the same protocol used for initial HCC, as recommended in the Japanese guidelines [1]. Basically, hepatectomy was indicated for HCC with one to three nodules, regardless of tumor size. If the tumor size was 3 cm or less, RFA was also indicated. Which treatment was chosen depended on the tumor location and the patient's condition. For tumors with four or more nodules, TACE was indicated. For distant metastasis, systemic therapy was applied.

Statistical analyses

Categorical and continuous data were compared between the groups using the chi-squared and Mann–Whitney U tests, respectively. Continuous data were presented as medians and ranges. Patient survival was compared using Kaplan–Meier curves, and differences in survival between the groups were analyzed using the log-rank test. Uni- and multivariate analysis were performed to detect the risk factors for early recurrence, and early and multiple recurrence using a logistic regression model, and for late recurrence using Cox regression model. Statistical significance was set at $p < 0.05$.

Results

Analysis according to the initial recurrence period (Study 1)

The preoperative demographic and clinical characteristics are shown in Table 1. The early recurrence group had a significantly higher AFP (76 vs. 11 ng/mL, $p=0.002$) and DCP (795 vs. 92 mAU/mL, $p=0.004$) levels, larger maximum tumor diameter (6.0 vs. 3.5 cm, $p<0.001$), higher rate of multiple tumors (45 vs. 20%, $p=0.002$), higher BCLC stage (0, A, B, and C: 3, 47, 29, and 21 vs. 12, 76, 11, and 1%, respectively; $p<0.001$), and higher rates of Up-to-7 criteria out (53 vs. 26%, $p=0.002$) and 5–5-500 criteria out (63 vs. 36%, $p=0.004$) than the late recurrence group, reflecting tumor biology.

Regarding surgical outcomes and histological examination of the resected specimen, the early recurrence group had a significantly longer operative time (353 vs. 303 min, $p=0.042$) and higher incidence of macrovascular PVTT (vp2 and 3: 11 and 14 vs. 0 and 0%, respectively; $p<0.001$) than the late recurrence group. Regarding recurrence patterns, the incidence of multiple nodular recurrences with ≥ three lesions or distant metastasis was significantly higher in the early recurrence group than in the late recurrence group (single, two nodules, ≥ three nodules, and distant metastasis: 24, 16, 40, and 21% vs. 47, 18, 33, and 3%, respectively; $p=0.001$). The treatments administered after recurrence showed significant variations between the early and late recurrent groups, including surgery, ablation, transarterial infusion chemotherapy (TAI) or transarterial chemoembolization (TACE), radiation, systemic chemotherapy and best supportive care (BSC) (8, 25, 50, 0, 11, and 6% vs. 21, 54, 20, 1, 5, and 0%, respectively; $p<0.001$). Particularly, the rate of local treatments including surgery, ablation, and radiation was significantly lower in the early recurrent group compared to the late recurrent group (33% vs. 76%, $p<0.001$; Table 2).

Postoperative overall survival (OS) was significantly lower in the early recurrence group than in the late recurrence group, with 5-year survival being 37 and 79%, respectively ($p<0.001$; Fig. 2a). The difference remained significant when survival was calculated from the time of initial recurrence, with 5-year survival being 31 and 66%, respectively ($p<0.001$; Fig. 2b).

When the risk factors preoperatively detectable for early recurrence within 6 months were evaluated in all HCC cases followed up at least 6 months ($n=285$), albumin level ($p=0.01$), maximum tumor diameter ($p<0.001$), multiple tumor nodules ($p=0.001$), BCLC stage ($p<0.001$), Up-to-7 criteria ($p<0.001$) and 5–5-500 criteria ($p=0.001$) were identified as risk factors in the univariate analysis. The maximum tumor diameter [odds ratio (OR) 1.12, 95% confidence interval (CI) 1.02–1.22,

Table 1 Preoperative characteristics of HCC patients with recurrence after hepatectomy according to recurrence period

	Early recurrence ($n=38$)	Late recurrence ($n=113$)	*p* value
Age	71 (38–84)	69 (38–86)	0.74
Gender (Male / Female)	30/8	96/17	0.39
BMI	22.7 (13.2–34.5)	22.9 (15.6–31.4)	0.87
Albumin (g/dL)	3.7 (2.3–4.6)	3.9 (2.3–5.0)	0.15
Total bilirubin (mg/dL)	0.7 (0.3–1.5)	0.7 (0.2–2.5)	0.39
PT-INR	1.06 (0.89–1.30)	1.05 (0.88–1.41)	0.55
Platelet count ($\times 10^4/\mu L$)	19.2 (6.2–179.0)	17.5 (4.3–259.7)	0.13
AFP (ng/mL)	**76 (2–605,100)**	**11 (1–242,000)**	**0.002**
DCP (mAU/mL)	**795 (15–174,400)**	**92 (10–51568)**	**0.004**
ICG R15 (%)	12.7 (3.7–68.6)	13.2 (1.6–49.9)	0.93
LHL15	0.934 (0.831–0.965)	0.930 (0.679–0.984)	0.96
PNI	45.1 (26.6–55.9)	45.9 (26.0–59.7)	0.40
Underlying liver disease NBNC / HBV / HCV	20 (53%) / 4 (11%) / 14 (37%)	37 (33%) / 15 (13%) / 61 (54%)	0.089
Maximum tumor diameter (cm)	**6.0 (1.8–20.0)**	**3.5 (0.5–26.0)**	**< 0.001**
Single / Multiple tumor nodules	**21 (55%) / 17 (45%)**	**91 (81%) / 22 (20%)**	**0.002**
BCLC stage 0/A/B/C	**1 (3%)/ 18 (47%)/ 11 (29%)/ 8 (21%)**	**14 (12%)/ 86 (76%)/ 12 (11%)/ 1 (1%)**	**< 0.001**
Up-to-7 criteria in / out	**18 (47%) / 20 (53%)**	**84 (74%) / 29 (26%)**	**0.002**
5–5-500 criteria in / out	**14 (37%) / 24 (63%)**	**72 (64%) / 41 (36%)**	**0.004**

BMI Body mass index, *PT-INR* Prothrombin time-international normalized ratio, *AFP* Alpha fetoprotein, *DCP* des-γ-carboxyprothrombin, *ICG R15* indocyanine green retention rate at 15 min, *LHL15* GSA uptake ratio of the liver to the liver plus heart at 15 min, *PNI* Prognostic nutritional index, *NBNC* Non-B non-C, *HBV* hepatits B, *HCV* hepatitis C, *BCLC stage* Barcelona Clinic Liver Cancer stage

Table 2 Postoperative surgical outcomes and histological findings of HCC patients with recurrence after hepatectomy according to recurrence period

	Early recurrence ($n=41$)	Late recurrence ($n=113$)	*p* value
Operation time (min)	**353 (167–983)**	**302.5 (137–648)**	**0.042**
Blood loss (ml)	960 (0–36000)	776 (0–14000)	0.52
Anatomical /non-anatomical resection	29 (76%) / 9 (24%)	68 (61%) / 44 (39%)	0.082
Open / Laparoscopic	31 (82%) / 7 (18%)	88 (78%) / 25 (22%)	0.63
T-Bil on POD5	1.05 (0.3–8.0)	1.0 (0.3–7.6)	0.59
PT-INR on POD 5	1.13 (0.94–1.51)	1.14 (0.95–1.88)	1.00
Complications (C-D > Grade 3)	4 (11%)	23 (21%)	0.21
Tumor differentiation (well, moderate. poor)	4 (11%) / 25 (68%) / 8 (22%)	27 (29%) / 54 (59%) / 11 (12%)	0.055
vp 0/1–3	**15 (42%) / 12 (33%) / 4 (11%) / 5 (14%)**	**56 (67%) / 28 (33%) / 0 / 0**	**< 0.001**
vv 0/1	33 (89%) / 4 (11%)	91 (96%) / 4 (4%)	0.22
Liver fibrosis (NL/CH/LC)	4 (13%) / 19 (63%) / 7 (23%)	7 (10%) / 36 (49%) / 31 (42%)	0.20
Recurrence pattern (single/two/3 or more/distant metastasis)	**9 (24%) / 6 (16%) / 15 (40%) / 8 (21%)**	**53 (47%) / 20 (18%) / 37 (33%) / 3 (3%)**	**0.001**
Surgery/ Ablation/ TAI, TACE / Radiation/ Systemic treatment/ BSC	**3 (8%) / 9 (25%) / 18 (50%) / 0 / 4 (11%) / 2 (6%)**	**22 (21%) / 60 (54%) / 22 (20%) / 1 (1%) / 5 (5%) / 0**	**< 0.001**
Local treatment (surgery, ablation, radiation) / Other treatment (TAI, TACE, systemic, BSC)	**12 (33%) / 24 (67%)**	**84 (76%) / 27 (24%)**	**< 0.001**
Surgery / Other treatment	3 (8%) / 33 (92%)	23 (21%) / 88 (79%)	0.091

T-Bil total bilirubin, *PT-INR* prothrombin time-international normalized ratio, *POD* postoperative day, *C-D* Clavien-Dindo, *vp* Portal vein invasion including microvascular invasion, *vv* Hepatic vein invasion including microvascular invasion, *NL* normal liver, *CH* chronic hepatitis, *LC* liver cirrhosis, *TAI* transarterial infusion chemotherapy, *TACE* transarterial chemoembolization, *BSC* best supportive care

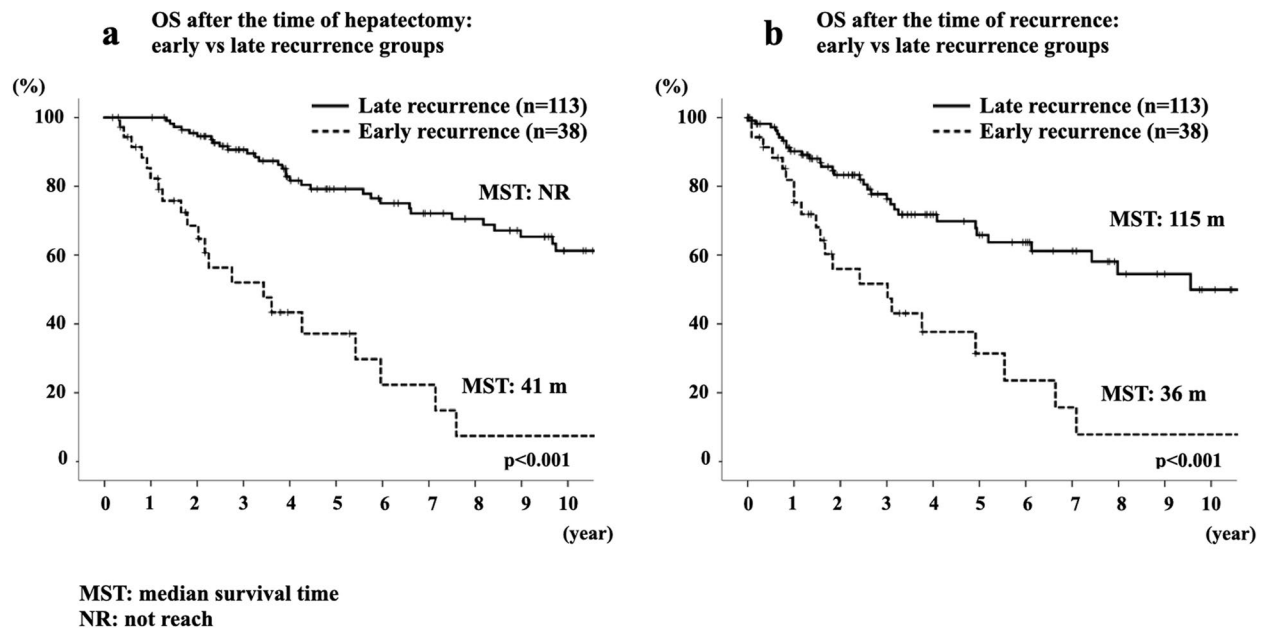

Fig. 2 Overall survival (OS) in patients with HCC recurrence after hepatectomy according to recurrence period. **a**: OS after the time of hepatectomy: early vs late recurrence groups. **b**: OS after the time of recurrence: early vs late recurrence groups

$p=0.013$] and BCLC stage (OR 7.87, 95% CI 2.28–27.03, $p=0.001$) were independent risk factors in multivariate analysis (Table 3). On the other hand, when the risk factors for late recurrence 6 months after surgery were evaluated in all HCC patients who survived for more than 6 months ($n=243$), PT-INR ($p=0.027$), LHL15 in GSA scintigram ($p=0.034$), PNI ($p=0.013$), underlying liver disease ($p=0.05$) and BCLC stage ($p=0.018$). The LHL15 in GSA scintigram was independent risk factors in multivariate analysis (HR 0.019, 95% CI 0.00–0.75, $p=0.034$) (Table 4).

Since BCLC stage and tumor size strongly affected early recurrence, we conducted subgroup analysis of survival based on BCLC stage and tumor size. OS after the time of recurrence was still significantly lower in the early recurrence group than in the late recurrence group among patients with BCLC stage 0 or A, with 5-year survival being 25 and 69%, respectively ($p<0.001$; Fig. 3a), but not significant in those with BCLC stage B or C (Fig. 3b). Tumor size was identified as another risk factor for early recurrence. The optimal cutoff value for tumor size was determined through receiver operating characteristic curve analysis as 3.85 cm (Fig. 3c). In survival analysis based on tumor size, OS after recurrence was significantly lower in the early recurrence group than the late recurrence group, both among patients with tumors smaller than 3.85 cm (5-year survival: 44 and 68%, respectively, $p=0.017$; Fig. 3d) and those with tumors measuring 3.85 cm or larger (5-year survival: 30 and 64%, respectively, $p=0.004$; Fig. 3e).

Analysis according to the number of initial recurrent tumors (Study 2)

The preoperative demographic and clinical characteristics are shown in Table 5. The multiple recurrence group had a significantly higher age (71 vs. 67.5, $p=0.02$), lower albumin level (3.7 vs. 4.0 g/dL, $p=0.018$) and PNI (44.7 vs. 47.3, $p=0.026$) and larger maximum tumor diameter (4.7 vs. 3.2 cm, $p=0.017$) than the single recurrence group. Regarding surgical outcomes and histological examination of the resected specimen, the multiple recurrence group had a significantly lower incidence

Table 3 Uni- and multivariate analysis of preoperative risk factors for early recurrence within 6 months among all HCC cases followed up for more than 6 months after initial hepatectomy

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	***p* value**	**OR (95% CI)**	***p* value**
Age	1.01 (0.98–1.05)	0.50		
Gender (Male / Female)	1.04 (0.45–2.39)	0.94		
BMI	0.99 (0.91–1.08)	0.82		
Albumin (g/dL)	**0.41 (0.21–0.81)**	**0.01**		
Total bilirubin (mg/dL)	1.30 (0.48–3.55)	0.61		
PT-INR	3.66 (0.15–90.6)	0.43		
Platelet count ($\times 10^4$/μL)	1.01 (1.00–1.01)	0.33		
AFP (ng/mL)	1.00 (1.00–1.00)	0.12		
DCP (mAU/mL)	1.00 (1.00–1.00)	0.50		
ICG R15 (%)	1.01 (0.99–1.04)	0.37		
LHL15	0.41 (0.00–974.25)	0.79		
PNI	0.95 (0.90–1.00)	0.051		
Underlying liver disease NBNC / HBV / HCV	1.30 (0.64–2.66)	0.47*		
Maximum tumor diameter (cm)	**1.19 (1.11–1.29)**	**< 0.001**	**1.12 (1.02–1.22)**	**0.013**
Multiple tumor nodules	**3.36 (1.69–6.66)**	**0.001**		
BCLC stage 0/A/B/C	**14.08 (4.55–43.48)**	**< 0.001***	**7.87 (2.28–27.03)**	**0.001****
Up-to-7 criteria out	**4.17 (2.11–8.20)**	**< 0.001**		
5–5-500 criteria out	**3.15 (1.59–6.24)**	**0.001**		
Anatomical resection	1.95 (0.89–4.27)	0.095		
Laparoscopic	0.57 (0.24–1.35)	0.20		

BMI body mass index, *PT-INR* prothrombin time-international normalized ratio, *AFP* alpha fetoprotein, *DCP* des-γ-carboxyprothrombin, *ICG R15* indocyanine green retention rate at 15 min, *LHL15* GSA uptake ratio of the liver to the liver plus heart at 15 min, *PNI* prognostic nutritional index, *NBNC* Non-B non-C, *HBV* hepatits B, *HCV* hepatitis C, *BCLC stage* Barcelona Clinic Liver Cancer stage

* The risk of NBNC to HCV

** The risk of BCLC stage C to stage A

Table 4 Uni- and multivariate analysis of preoperative risk factors for recurrence among all HCC cases who survived more than 6 months after initial hepatectomy

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	***p* value**	**HR (95% CI)**	***p* value**
Age	1.02 (1.00–1.04)	0.078		
Gender (Male / Female)	0.82 (0.52–1.30)	0.40		
BMI	0.97 (0.92–1.02)	0.21		
Albumin (g/dL)	0.70 (0.48–1.02)	0.06		
Total bilirubin (mg/dL)	1.15 (0.66–2.01)	0.64		
PT-INR	**6.18 (1.23–31.10)**	**0.027**		
Platelet count ($\times 10^4$/μL)	1.00 (0.99–1.01)	0.46		
AFP (ng/mL)	1.00 (1.00–1.00)	0.63		
DCP (mAU/mL)	1.00 (1.00–1.00)	0.44		
ICG R15 (%)	1.04 (1.00–1.03)	0.061		
LHL15	**0.019 (0.00–0.75)**	**0.034**	**0.019 (0.00–0.75)**	**0.034**
PNI	**0.96 (0.93–0.99)**	**0.013**		
Underlying liver disease NBNC / HBV / HCV	**0.69 (0.47–1.00)**	**0.05***		
Maximum tumor diameter (cm)	1.03 (0.98–1.08)	0.25		
Multiple tumor nodules	1.41 (0.93–2.15)	0.11		
BCLC stage 0/A/B/C	**2.37 (1.16–4.82)**	**0.018****		
Up-to-7 criteria out	1.29 (0.88–1.89)	0.20		
5–5-500 criteria out	1.01 (0.71–1.44)	0.97		
Anatomical resection	0.84 (0.59–1.21)	0.35		
Laparoscopic	1.23 (0.80–1.89)	0.35		

BMI body mass index, *PT-INR* prothrombin time-international normalized ratio, *AFP* alpha fetoprotein, *DCP* des-γ-carboxyprothrombin, *ICG R15* indocyanine green retention rate at 15 min, *LHL15* GSA uptake ratio of the liver to the liver plus heart at 15 min, *PNI* prognostic nutritional index, *NBNC* Non-B non-C, *HBV* hepatits B, *HCV* hepatitis C, *BCLC stage* Barcelona Clinic Liver Cancer stage

* The risk of NBNC to HCV

** The risk of BCLC stage B to stage 0

of well-differentiated tumors (13 vs. 41%, $p=0.001$) and liver cirrhosis (26 vs. 50%, $p=0.03$) than the single recurrence group. The treatments administered after recurrence showed significant variations between the single and multiple recurrent groups, including surgery, ablation, TAI or TACE, radiation, systemic chemotherapy and BSC (23, 63, 10, 0, 2, and 2% vs. 14, 36, 39, 1, 8, and 1%, respectively; $p<0.001$). Particularly, the rate of local treatments including surgery, ablation, and radiation was significantly higher in the single recurrent group compared to the multiple recurrent group (87% vs. 51%, $p<0.001$; Table 6).

The postoperative OS was significantly lower in the multiple recurrence group than in the single recurrence group, with 5-year survival being 58 and 85%, respectively ($p=0.001$; Fig. 4a). The difference remained significant when survival was calculated from the time of initial recurrence, with 5-year survival being 47 and 72%, respectively ($p=0.005$; Fig. 4b). When the multiple recurrence group was divided into detailed three subgroups: those with two lesions ($n=26$), those with ≥ three lesions ($n=52$), and those with distant metastases ($n=11$), and they were compared with the single recurrence group, both OS after operation and OS after initial recurrence were significantly lower as the number of tumors increased, with 5-year survival being 85, 88, 47, and 31% ($p<0.001$) and 72, 88, 28, and 36% ($p<0.001$), respectively (Fig. 4c, d). The time to recurrence after surgery was significantly shorter in the multiple recurrence group than in the single recurrence group, with median recurrence-free survival times (MRFS) being 11 and 22 months, respectively ($p=0.003$; Fig. 4e). When comparing the four subgroups according to the number of recurrent tumors, the differences remained significant as the number of tumors increased, with MRFS being 22, 17, 11, and 5 months ($p<0.001$), respectively (Fig. 4f).

Survival analysis according to the combination of initial recurrence period and the number of recurrent tumors (Study 3)

To identify the subgroup with the poorest prognosis, we categorized patients into three groups based on the

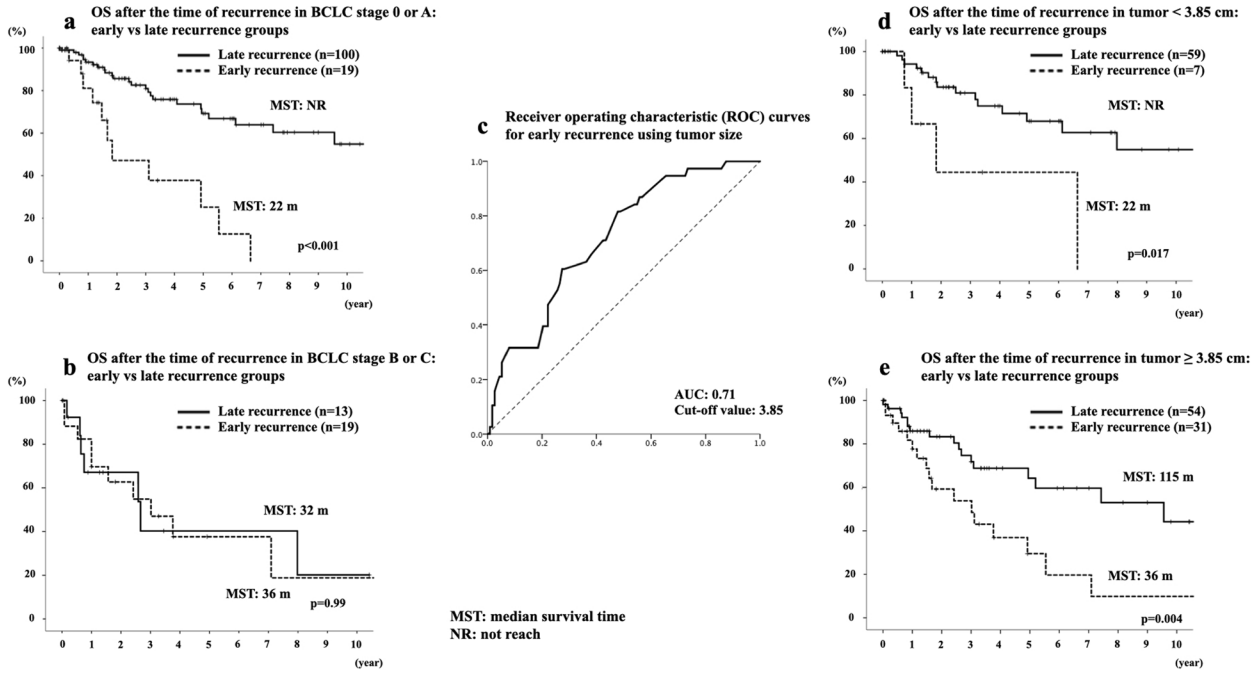

Fig. 3 Overall survival (OS) in patients with HCC recurrence after hepatectomy, according to recurrence period in subgroup based on BCLC stage and tumor size. **a**: OS after the time of recurrence in BCLC stage 0 or A: early vs late recurrence groups. **b**: OS after the time of recurrence in BCLC stage B or C: early vs late recurrence groups. **c**: Receiver operating characteristic (ROC) curves for early recurrence using tumor size. **d**: OS after the time of recurrence in tumor < 3.85 cm: early vs late recurrence groups. **e**: OS after the time of recurrence in tumor ≥ 3.85 cm: early vs late recurrence groups

Table 5 Preoperative characteristics of HCC patients with recurrence after hepatectomy according to recurrence type

	Single recurrence (*n* = 62)	**Multiple recurrence (*n* = 89)**	***p* value**
Age	**67.5 (38–85)**	**71 (38–86)**	**0.02**
Gender (Male / Female)	52/10	74/15	0.91
BMI	22.9 (15.8–33.7)	22.9 (13.2–34.5)	0.69
Albumin (g/dL)	**4.0 (2.4–5.0)**	**3.7 (2.3–4.9)**	**0.018**
Total bilirubin (mg/dL)	0.8 (0.2–1.7)	0.6 (0.2–2.5)	0.36
PT-INR	1.06 (0.88–1.41)	1.06 (0.89–1.41)	0.87
Platelet count ($\times 10^4$/μL)	17.5 (4.3–264.0)	17.9 (4.4–179.0)	0.43
AFP (ng/mL)	13 (1–41,875)	15 (2–605,100)	0.59
DCP (mAU/mL)	71 (12–51,568)	347 (10–174400)	0.064
ICG R15 (%)	13.2 (3.9–42.3)	12.9 (1.6–68.6)	0.98
LHL15	0.93 (0.68–0.98)	0.93 (0.75–0.98)	0.15
PNI	**47.3 (29.1–59.7)**	**44.7 (26.0–57.0)**	**0.026**
Underlying liver disease NBNC / HBV / HCV	19 (31%) / 12 (19%) / 31 (50%)	38 (34%) / 7 (8%) / 44 (49%)	0.073
Maximum tumor diameter (cm)	**3.2 (0.5–26.0)**	**4.7 (1.0–20.0)**	**0.017**
Single / Multiple tumor nodules	48 (77%) / 14 (23%)	64 (72%) / 25 (28%)	0.45
BCLC stage 0/A/B/C	7 (11%)/ 47 (76%)/ 6 (10%)/ 2 (3%)	8 (9%)/ 57 (64%)/ 17 (19%)/ 7 (8%)	0.22
Up-to-7 criteria in / out	44 (71%) / 18 (29%)	58 (65%) / 31 (35%)	0.45
5–5-500 criteria in / out	38 (61%) / 24 (39%)	48 (54%) / 41 (45%)	0.37

BMI body mass index, *PT-INR* prothrombin time-international normalized ratio, *AFP* alpha fetoprotein, *DCP* des-γ-carboxyprothrombin, *ICG R15* indocyanine green retention rate at 15 min, *LHL15* GSA uptake ratio of the liver to the liver plus heart at 15 min, *PNI* prognostic nutritional index, *NBNC* Non-B non-C, *HBV* hepatits B, *HCV* hepatitis C, *BCLC stage* Barcelona Clinic Liver Cancer stage

Table 6 Postoperative surgical outcomes and histological findings of HCC patients with recurrence after hepatectomy according to recurrence type

	Single recurrence (*n* = 62)	**Multiple recurrence (*n* = 89)**	***p* value**
Operation time (min)	282 (157–983)	333 (137–648)	0.19
Blood loss (ml)	803 (0–36000)	866 (0–14000)	0.87
Anatomical /non-anatomical resection	39 (63%) / 23 (37%)	58 (66%) / 30 (34%)	0.71
T-Bil on POD5	0.95 (0.4–3.4)	1.0 (0.3–8.0)	0.85
PT-INR on POD 5	1.13 (0.95–1.88)	1.14 (0.94–1.51)	0.39
Complications (C-D > Grade 3)	14 (23%)	13 (15%)	0.22
Tumor differentiation (well, moderate. poor)	**21 (41%) / 23 (45%) / 7 (14%)**	**10 (13%) / 56 (72%) / 12 (15%)**	**0.001**
vp 0/1–3	35 (71%) / 13 (27%) / 0 / 1 (2%)	36 (51%) / 27 (38%) / 4 (6%) / 4 (6%)	0.075
vv 0/1	49 (94%) / 3 (6%)	75 (94%) / 5 (6%)	0.91
Liver fibrosis (NL/CH/LC)	**5 (11%) / 18 (39%) / 23 (50%)**	**6 (10%) / 37 (64%) / 15 (26%)**	**0.03**
Surgery/ Ablation/ TAI, TACE / Radiation/ Systemic treatment/ BSC	**14 (23%) / 38 (63%) / 6 (10%) / 0 / 1 (2%) / 1 (2%)**	**12 (14%) / 31 (36%) / 34 (39%) / 1 (1%) / 8 (9%) / 1 (1%)**	**< 0.001**
Local treatment (surgery, ablation, radiation) / Other treatment (TAI, TACE, systemic, BSC)	**52 (87%) / 8 (13%)**	**44 (51%) / 43 (49%)**	**< 0.001**
Surgery / Other treatment	14 (23%) / 46 (77%)	12 (14%) / 75 (86%)	0.14

T-Bil total bilirubin, *PT-INR* prothrombin time-international normalized ratio, *POD* postoperative day, *C-D* Clavien-Dindo, *vp* Portal vein invasion including microvascular invasion, *vv* Hepatic vein invasion including microvascular invasion, *NL* normal liver, *CH* chronic hepatitis, *LC* liver cirrhosis, *TAI* transarterial infusion chemotherapy, *TACE* transarterial chemoembolization, *BSC* best supportive care

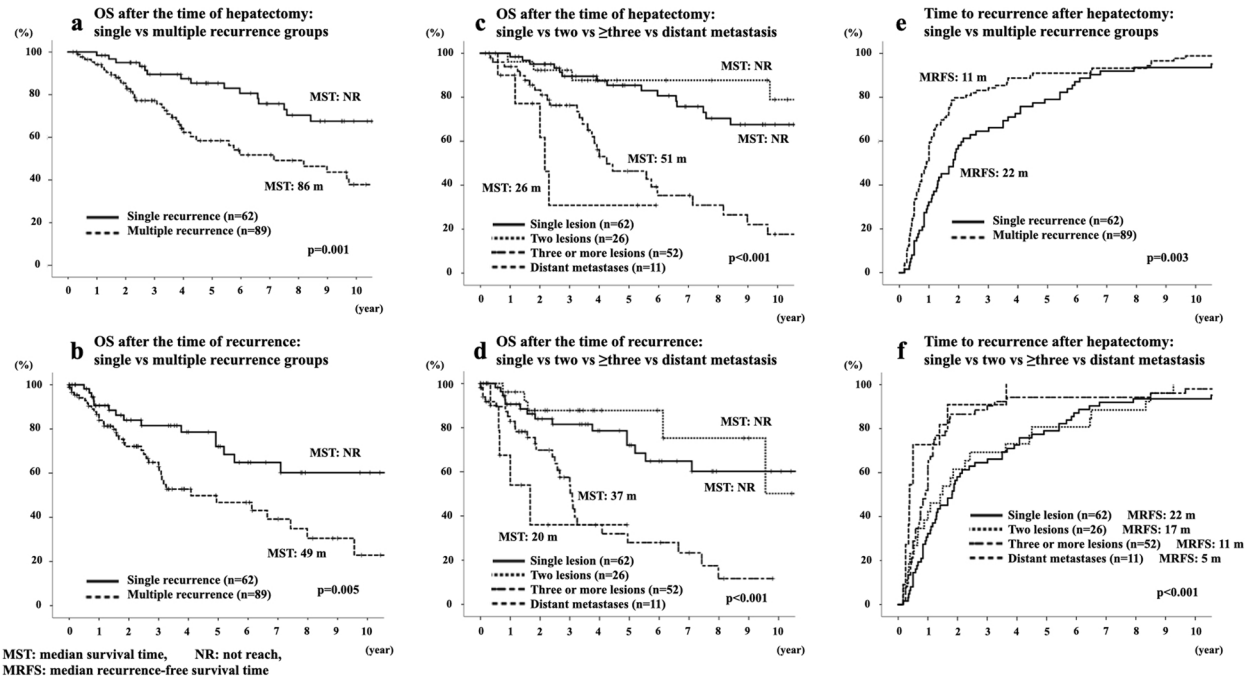

Fig. 4 Overall survival (OS) and time to recurrence after surgery in patients with HCC recurrence after hepatectomy according to the number of initial recurrent tumors. **a**: OS after the time of hepatectomy: single vs multiple recurrence groups. **b**: OS after the time of recurrence: single vs multiple recurrence groups. **c**: OS after the time of hepatectomy: single vs two vs ≥ three vs distant metastasis. **d**: OS after the time of recurrence: single vs two vs ≥ three vs distant metastasis. **e**: Time to recurrence after hepatectomy: single vs multiple recurrence groups. **f**: Time to recurrence after hepatectomy: single vs two vs ≥ three vs distant metastasis

recurrence period and the number of recurrent tumors: late recurrence with one or two tumors (Group A; $n=74$), early recurrence or three or more tumors or distant metastasis (Group B; $n=54$), and early recurrence with three or more tumors or distant metastasis (Group C; $n=23$). According to the findings of Study 2, a cut-off value of three recurrent tumors or more was applied to indicate a poor prognosis. OS was effectively stratified, demonstrating significantly lower survival rates in Groups B and C compared to Group A, both following hepatectomy (5-year survival in Group A, B, and C: 91%, 55%, and 17%, respectively, $p<0.001$; Fig. 5a) and after recurrence (5-year survival in Group A, B, and C: 84%, 36%, and 17%, respectively, $p<0.001$; Fig. 5b).

Survival analysis stratified by the type of treatment for initial recurrence (Study 4)

Since the type of treatment for initial recurrence was another factor affecting patient survival, we conducted a survival analysis among two subgroups: one with local treatments including surgery, ablation, and radiation, and the other with non-local treatments including TAI, TACE, systemic treatment, and BSC. In patients receiving local treatments, OS was significantly lower as the number of tumors increased, with 5-year survival rates of 77%, 94%, 43%, and 0% for single, two, three or more tumors and distant metastases, respectively ($p<0.001$) (Fig. 6c). However, OS did not differ between the early and late recurrence groups (Fig. 6a). On the other hand, in patients receiving non-local treatments, OS was significantly lower in the early recurrence group than in the late recurrence group, with 5-year survival rates of 16% and 42%, respectively ($p=0.015$; Fig. 6b). However, OS did not differ by the number of recurrent nodules (Fig. 6d). When patients were classified by the combination of recurrence period and number according to the manner of Study 3, OS was effectively stratified, demonstrating significantly lower survival in Groups B and C compared to Group A, both in the local treatment subgroup (5-year survival in Groups A, B, and C: 83%, 51%, and 25%, respectively, $p<0.001$; Fig. 6e) and the non-local treatment subgroup (5-year survival in Groups A, B, and C: 86%, 15%, and 14%, respectively, $p=0.017$; Fig. 6e).

Uni- and multivariate analysis of preoperative risk factors for early and multiple recurrence (Study 5)

We aimed to identify preoperative risk factors for cases that would potentially recur within 6 months and develop 3 or more nodules (Group C), which are associated with the poorest prognosis as described in previous analyses. Among all HCC cases who underwent initial hepatectomy and were followed up for at least 6 months ($n=285$), albumin level ($p=0.01$), PNI ($p=0.021$), maximum tumor diameter ($p=0.002$), BCLC stage ($p=0.001$), Up-to-7 criteria ($p=0.005$), and 5–5-500 criteria ($p=0.003$) were identified as risk factors for recurrence within 6 months and with 3 or more nodules in univariate analysis. In multivariate analysis, the BCLC stage was the only independent risk factor for recurrence within 6 months and with 3 or more nodules (Table 7).

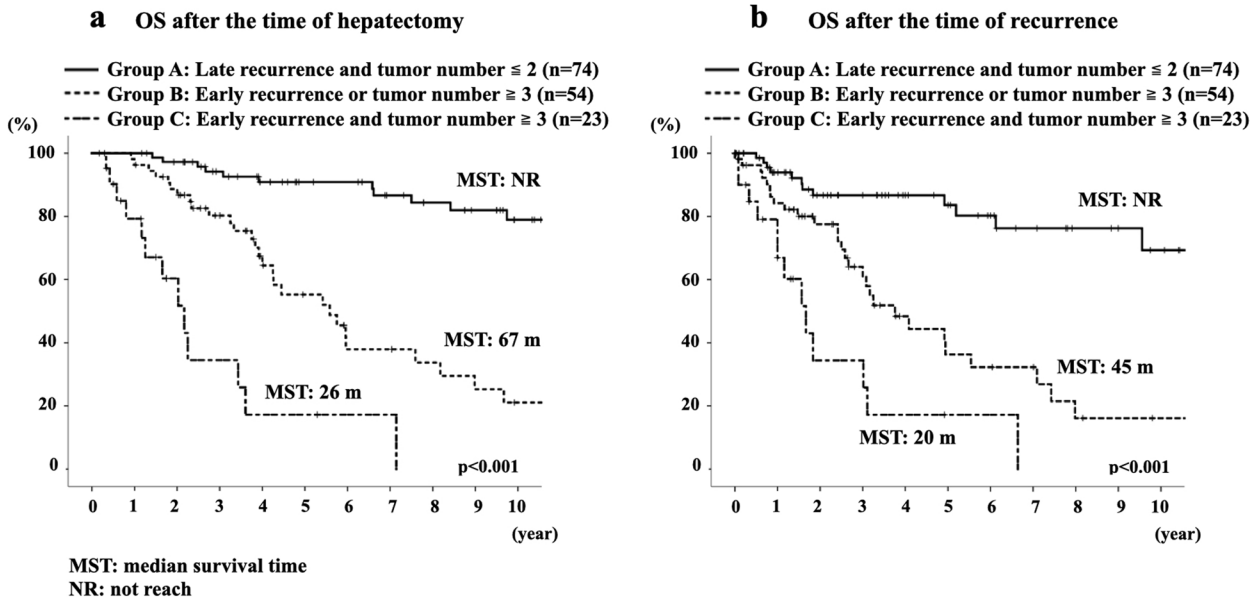

Fig. 5 Overall survival (OS) in patients with HCC recurrence after hepatectomy according to the combination of recurrence period and the number of initial recurrent tumors. **a**: OS after the time of hepatectomy. **b**: OS after the time of recurrence

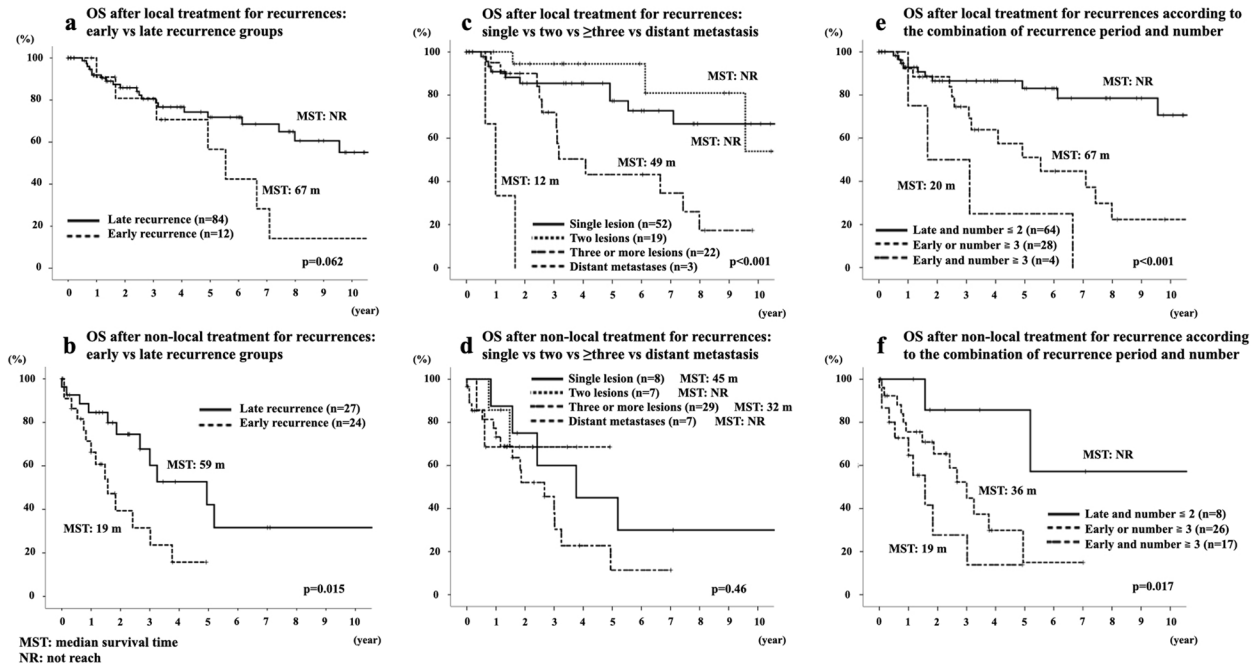

Fig. 6 Overall survival (OS) after surgery in patients with HCC recurrence after hepatectomy, according to recurrence pattern in subgroup based on post-recurrence treatment. **a**: OS after local treatment for recurrences: early vs late recurrence groups. **b**: OS after non-local treatment for recurrences: early vs late recurrence groups. **c**: OS after local treatment for recurrences: single vs two vs ≥ three vs distant metastasis. **d**: OS after non-local treatment for recurrences: single vs two vs ≥ three vs distant metastasis. **e**: OS after local treatment for recurrences according to the combination of recurrence period and number. **f**: OS after non-local treatment for recurrence according to the combination of recurrence period and number

Discussion

In the present study, advanced tumor stage and longer operative time were the risk factors for early recurrence after curative hepatectomy for initial HCC. The early recurrence group exhibited poor OS not only following surgery but also after the time of recurrence. In multivariate analysis in all HCC cases, tumor size and BCLC stage were independent risk factors for early recurrence. On the other hand, patients with multiple recurrent nodules also had a poorer OS and shorter time to recurrence, especially those with ≥ three nodules or distant metastases. The group with a combination of early recurrence and multiple nodular recurrences (≥ three) exhibited the poorest survival.

Biological tumor properties, including tumor markers (AFP and DCP), tumor size, multiple nodules, and microvascular PVTT, with advanced tumor stage were risk factors for early recurrence after hepatectomy for HCC, as precious studies had shown [14–20]. Tumor cells may already be present in the remnant liver or bloodstream of patients with potential malignant tumors before hepatectomy in cases with advanced stage. In the present study, operative time was another factor that affected early recurrence. Operative time can be affected by many factors, including the surgical procedure, tumor location, liver condition, open or laparoscopic surgical approach, and the surgeon's experience. The most influential factor is likely the surgical procedure, because the early recurrence group had a significantly higher rate of multiple tumors and large tumors. Liver resection in multiple areas and handling of large tumors might contribute to longer operative times. A previous study also reported that blood loss and operative time were found to be risk factors for early recurrence [21]. Another study suspected that portal vein clamp during hepatectomy induce early HCC recurrence owing to liver ischemic-reperfusion injury (IRI) [22]. A longer operative time may cause IRI through repeated Pringle maneuvers, thus inducing early recurrence.

Regarding the analysis of the recurrence patterns, tumor diameter and PNI were risk factors for multiple nodular recurrences among the preoperatively detectable patient factors. Although previous studies showed some risk factors like tumor marker and size for multiple recurrences [23], no studies have assessed the relationship between immunonutritional/inflammatory indices and recurrence pattern. On the other hand, impaired host immunity like sarcopenia was related to tumor recurrence in HCC [24]. We also previously reported that patients with low PNI had lower OS and progression-free

Table 7 Uni- and multivariate analysis of preoperative risk factors for recurrence with within 6 months and with 3 or more nodules among all HCC cases who underwent initial hepatectomy

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	***p* value**	**OR (95% CI)**	***p* value**
Age	1.00 (0.96–1.05)	0.99		
Gender (Male / Female)	0.78 (0.26–2.35)	0.65		
BMI	1.01 (0.91–1.12)	0.85		
Albumin (g/dL)	**0.35 (0.15–0.77)**	**0.01**		
Total bilirubin (mg/dL)	0.93 (0.25–3.38)	0.91		
PT-INR	5.73 (0.12–271.2)	0.38		
Platelet count ($\times 10^4$/μL)	1.00 (1.00–1.02)	0.13		
AFP (ng/mL)	1.00 (1.00–1.00)	0.073		
DCP (mAU/mL)	1.00 (1.00–1.00)	0.31		
ICG R15 (%)	1.02 (0.98–1.05)	0.35		
LHL15	5.60 (0.00–160354)	0.74		
PNI	**0.92 (0.87–0.99)**	**0.021**		
Underlying liver disease NBNC / HBV / HCV	0.92 (0.38–2.27)	0.86*		
Maximum tumor diameter (cm)	**1.18 (1.08–1.28)**	**0.002**		
Multiple tumor nodules	1.87 (0.79–4.41)	0.16		
BCLC stage 0/A/B/C	**37.7 (4.04–351.83)**	**0.001****	**37.7 (4.04–351.83)**	**0.001****
Up-to-7 criteria out	**3.26 (1.44–7.40)**	**0.005**		
5–5-500 criteria out	**3.71 (1.56–8.86)**	**0.003**		
Anatomical resection	2.19 (0.80–6.00)	0.13		
Laparoscopic	0.37 (0.11–1.28)	0.12		

BMI body mass index, *PT-INR* prothrombin time-international normalized ratio, *AFP* alpha fetoprotein, *DCP* des-γ-carboxyprothrombin, *ICG R15* indocyanine green retention rate at 15 min, *LHL15* GSA uptake ratio of the liver to the liver plus heart at 15 min, *PNI* prognostic nutritional index, *NBNC* Non-B non-C, *HBV* hepatits B, *HCV* hepatitis C, *BCLC stage* Barcelona Clinic Liver Cancer stage

* The risk of NBNC to HCV

** The risk of BCLC stage C to stage 0

survival after hepatectomy for HCC and that PNI was an independent prognostic factor for OS [25]. Patients with a low PNI may have higher carcinogenesis, resulting in multiple nodular recurrences. A previous study also showed that disseminated HCC recurrence, defined as the presence of > 10 nodules in the bilateral lobes and a total tumor size of > 10 cm within 3 months after hepatectomy, was associated with a higher incidence of poor tumor grade and PVTT [15].

In the survival analysis, the patients with early recurrence and multiple recurrence showed poor prognosis not only following surgery but also after recurrence. On the other hand, the early recurrence group exhibited significantly advanced-stage tumors, particularly in terms of BCLC stage and tumor size, according to multivariate analysis. These factors were deemed to strongly influence postoperative survival. Nonetheless, early recurrence remained a significant factor for survival stratification even within subgroups characterized by early BCLC stage and tumor size. We found the relationship between the recurrence period and pattern, because the early recurrence often arose as multiple nodule recurrence, while multiple nodular recurrence showed shorter time to recurrence. These relationships have not been well discussed in previous reports. In a more detailed analysis, the group with ≥ three recurrent tumor nodules exhibited significantly poorer survival, whereas the groups with single and two nodules showed similar survival. The optimal cutoff value for the number of recurrent tumors was suspected to be three in predicting prognosis after recurrence. In a previous study, patients with ≥ three [26] or four [23] recurrent nodules exhibited significantly lower OS after resection. Based on our results, we developed a new classification system combining recurrence period and pattern shown in Fig. 5, which effectively stratified the survival curve. There have been no studies conducting such analysis before. It is speculated that these survival differences may be attributed to the tumor origin, whether it is a newly developed MO or IM from the primary site. In previous studies, IM was considered to arise within 2 years postoperatively [27] and as multiple nodular recurrences [28], whereas MO to arise > 2 years.

In our study, multivariate analysis also showed that the risk factor for early recurrence was BCLC stage, reflecting advanced tumor stage, while the risk factor for late recurrence was LHL15 in GSA scintigram, reflecting liver function. These findings suggest that the mechanisms of recurrence differ between early and late periods. Early recurrence might develop from remnant tumor cells after hepatectomy for advanced stage HCC as IM, while late recurrence might arise in the liver with impaired liver function, such as chronic hepatitis or cirrhosis as MO. On the other hand, the incidence of liver cirrhosis was significantly higher in the single nodular recurrence group, suggesting that they had originated in the fibrotic liver as MO. A previous study also showed that liver cirrhosis was highly associated with MO recurrence [28]. These findings also support the hypothesis that single recurrence tends to be MO and multiple recurrence tends to be IM.

Regarding treatment after recurrence, both early and multiple recurrences tended to be treated with non-curative modalities such as TACE or systemic therapy, while single and late recurrences were treated with local therapies such as surgery or ablation. Multiple recurrences with more than four nodules were typically treated with TACE according to Japanese guidelines. Additionally, the reason the early recurrence group had a lower rate of local treatment was considered that they had a higher rate of multiple nodular HCCs or distant metastasis. These differences in treatment after recurrence might affect survival rates. In previous studies, similar outcomes were observed between hepatectomy and RFA as a local treatment of recurrent tumors [29]. To eliminate the treatment bias, we performed a survival analysis in the subgroups of local and non-local treatments. The recurrence period remained a significant prognostic factor in the non-local treatment subgroup, while the number of recurrent nodules was a prognostic factor in the local treatment subgroup. When the recurrence period and number were combined, OS was well stratified in both the local and non-local treatment subgroups. This new classification system is considered a valuable approach capable of predicting prognosis after recurrence regardless of the treatment method.

Currently, systemic therapies using molecular-targeted agents and immune checkpoint inhibitors (ICIs) have been developed to treat HCC. As the adjuvant therapy, an RCT of ICIs using atezolizumab plus bevacizumab (IMbrave 050 Phase III trial) after curative resection or ablation showed survival benefit in recurrence free survival, while sorafenib had no survival benefit [30]. A meta-analysis of RCTs on adoptive immunotherapy showed significant improvement for OS and recurrence-free survival after curative treatment in the early stage (< 3 years) but not in the late stage (5 years) [31]. This result indicates that adjuvant immunotherapy may eliminate small IM but not prevent multicentric recurrence in the cirrhotic remnant liver. If adjuvant treatment is administered to groups at a high risk of IM, it may prevent recurrence and prolong survival. Preoperative prediction of the recurrence patterns of IM and MO is considered important in selecting high-risk groups. As an alternative method, assessing recurrence time and patterns may help us judge the high-risk population to be treated systemically. Based on the result from present study, the patients with intrahepatic recurrence of three or more nodules within 6 months after surgery may be a candidate to receive adjuvant treatment as IM rather than MO. Moreover, we found the BCLC stage was preoperative predictive factor for this poor prognostic subgroup in multivariate analysis. However, we could not histologically confirm the tumor origin at the recurrence site. Further studies are needed to histologically and genetically clarify the relationship between recurrence patterns and tumor origin.

Conclusions

In conclusion, advanced-stage HCC is associated with an increased risk of early recurrence and multiple or distant tumor recurrences after curative hepatectomy. Multiple tumor recurrences with ≥ three nodules tended to occur earlier postoperatively than single or two nodular recurrences. Patients with combined early and multiple or distant tumor recurrences exhibited a particularly poor survival after initial recurrence, irrespective of subsequent treatment. They should be carefully followed up, considering the possibility of IM rather than MO.

Ethics approval and consent to participate

All experimental protocols were reviewed and approved by Medical Ethics Committee of Mie University Hospital (H2021-156). This study was informed to all participants by opt-out on website of our institution instead of obtaining written consent form from the participants because of observational study. All participants were given the opportunity to reject their enrollment to this study. This procedure was approved by the Ethics Committee of the Mie University Hospital.

Consent for publication

This manuscript does not contain individual details about images or clinical data. Therefore, all participants were informed by opt-out on website of our institution instead of obtaining written consent form because of observational study. All participants were given the opportunity to reject their enrollment to this study. This procedure

was approved by the Ethics Committee of the Mie University Hospital.

Abbreviations:

AFP	Alpha fetoprotein
BCLC stage	Barcelona Clinic Liver Cancer stage
BSC	Best supportive care
CT	Computed tomography
DCP	Des-γ-carboxyprothrombin
GSA	Acid-galactosyl-human serum albumin
HCC	Hepatocellular carcinoma
ICGR15	Indocyanine green retention retention test at 15 min
ICIs	Immune checkpoint inhibitors
IM	Intrahepatic metastases
IRI	Ischemic-reperfusion injury
KICG	A plasma disappearance rate of ICG
LHL15	GSA uptake ratio of the liver to the liver plus heart at 15 min
MO	Metachronous multicentric occurrence
MRI	Magnetic resonance imaging
MRT	Mean recurrence times
OS	Overall survival
PNI	Prognostic nutritional index
POD	Postoperative day
PT-INR	Prothrombin time international normalized ratio
PVTT	Portal vein tumor thrombus
RCT	Randomized controlled trial (RCT)
RFA	Radiofrequency ablation
TACE	Transarterial chemoembolization
TAI	Transarterial infusion chemotherapy

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Authors' contributions
All authors helped to perform the research. All authors have read and approved the manuscript. Akihiro Tanemura: manuscript writing, data collection and data analysis Daisuke Noguchi, Toru Shinkai, Takahiro Ito, Aoi Hayasaki, Kazuyuki Gyoten, Takehiro Fujii, Yusuke Iizawa, Yasuhiro Murata, Naohisa Kuriyama and Masashi Kishiwada: contribution to writing the manuscript. Shugo Mizuno: contribution to writing the manuscript, drafting conception and design.

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Data availability
The data that support the findings of this study are available from the corresponding author, [AT], upon reasonable request.

Declarations

Competing interests
The authors declare no competing interests.

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