# Hepatectomy is Beneficial in Select Patients with Multiple Hepatocellular Carcinomas

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**Running head**: Surgery for multiple hepatocellular carcinoma

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**Synopsis**: The study reviewed liver resection procedures for multiple hepatocellular carcinomas.

**ABSTRACT**

**Background**: A single hepatocellular carcinoma (HCC) is a good indication for hepatic resection regardless of tumor size, but the surgical indications for cases with multiple HCCs remain unclear.

**Methods**: We retrospectively reviewed the outcomes of hepatectomies for Barcelona Clinic Liver Cancer (BCLC) Stage 0, A, and B HCCs. We further sub-classified Stage A and B into A1 (single <5 cm or ≤3 nodules ≤3 cm), A2 (single 5-10 cm), A3 (single ≥10 cm), B1 (2-3 nodules over 3 cm) and B2 (nodule number ≥4).

**Results**: A total of 1088 patients were enrolled, comprising 88 Stage 0, 750 Stage A (A1:485, A2:190, A3:75), and 250 Stage B (B1:166, B2:84) cases. The 5-year overall survival (OS) rates for Stage 0, A1, A2, A3, B1, and B2 patients were 70.4%, 74.2%, 63.8%, 47.7%, 47.5%, and 31.9%, respectively (P<0.0001). Significant differences in the OS were found between A1 and A2 (P=0.0118), A2 and A3 (P=0.0013), and B1 and B2 (P=0.0050), but not between A3 and B1 (P=0.4742). In the Stage B1 patients, multivariate analysis indicated that Child-Pugh B cirrhosis was the only independent prognostic factor for the OS outcome.

**Conclusions**: A hepatectomy should be considered for multiple HCC if the tumor number is three or less, especially in patients with no cirrhosis or in Child-Pugh A cases, because the long-term results are equivalent to those for a single HCC.

**Introduction**

Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death and currently ranks sixth globally in terms of tumor incidence [1]. Hepatic resection is the established treatment of choice for HCC as a potentially curative therapy among several treatment options such as resection, liver transplantation, local ablation, transarterial chemoembolization (TACE), and systemic therapy [2]. However, the surgical indications for HCC differ between Western and East-Asian countries. The European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) recommend the Barcelona Clinic Liver Cancer (BCLC) staging system for the management of HCC [2, 3]. According to this staging system, liver resection is only indicated for a single HCC of BCLC Stages 0 or A. On the other hand, the Asian Pacific Association for the Study of the Liver (APASL) and the Japan Society of Hepatology (JSH) do not necessarily limit the indications for hepatic resection to solitary HCC cases [4, 5].

Many prior reports have also suggested that hepatic resection should be indicated for a single HCC even if large in size [6, 7]. These studies have indicated that liver resection is an effective treatment for a single HCC of any size. In the case of multiple HCCs, it has been reported that hepatic resections yield satisfactory results if they fall within the Milan criteria [8]. In contrast, the effectiveness of these surgeries for multiple HCCs beyond the Milan criteria, in other words cases of an intermediate stage (BCLC Stage B), is controversial and

remains unclear.

In our present study, we examined the long-term outcomes among Japanese liver resection cases in accordance with the BCLC stage. We retrospectively reviewed a cohort of BCLC Stage 0, A, and B HCC patients who underwent liver resection at our institution over a 30 year period. We conducted further subclassifications, analyzed the surgical outcomes, and investigated the validity of hepatic resection for multiple HCCs in comparison to single HCC cases.

**Patients and Methods**

Between 1991 and 2020, 1088 patients comprising very early (BCLC stage 0), early (BCLC stage A) or intermediate (BCLC stage B) stage HCCs underwent a liver resection at the Department of Gastroenterological Surgery I, Hokkaido University Hospital. A modified BCLC staging system was used for these patients as follows: BCLC 0 was defined as a single tumor ≤2 cm; BCLC A as a single tumor >2 cm, or two to three nodules, all <3 cm; and BCLC B as two to three nodules ≥ 3 cm or ≥ 4 nodules. [2, 3]. In our present analyses, we further subclassified the patients in the study cohort into five groups as follows: stage 0 (single nodule ≤2 cm), stage A1 (single 2-5 cm or ≤3 nodules ≤3 cm), stage A2 (single 5-10 cm), stage A3 (single ≥10 cm), stage B1 (2-3 nodules over 3 cm), and stage B2 (nodule number ≥4). All cases had received a pathological diagnosis of HCC and any cases of

pathological necrosis were excluded.

This study was approved by the institutional review board of Hokkaido University Hospital (approval number: 021-0075). All analyses were performed in accordance with the ethical guidelines of Hokkaido University Hospital.

**Preoperative management**

The surgical indications in our present study series were determined using an algorithm we developed and described previously [9]. The absence of uncontrolled ascites and a total bilirubin level of less than 2 mg/dl were required criteria for a subsequent hepatectomy. The specific liver resection procedure was then determined by measuring the indocyanine green retention rate at 15 minutes (ICGR15) and remnant liver volume by volumetric computed tomography (CT) prior to surgery.

**Surgical methods**

We have previously described the surgical methods used for the liver resection [9]. An intraoperative ultrasound was performed in all patients. Transection of the liver parenchyma was conducted using the hook spatula of an ultrasonic harmonic scalpel (Ethicon EndoSurgery, San Angelo, TX) and either a DS3.0 Dissecting Sealer (Medtronic, Minneapolis, MN) or a bipolar cautery with a saline irrigation system. Inflow occlusion was

applied in an intermittent manner with 15 minutes of occlusion alternating with 5 minutes of reperfusion. We defined anatomical resection in our current study as the complete removal of the lesion based on Couinaud's classification.

**Postoperative management**

Follow-up studies using CT or magnetic resonance imaging and the measurement of alpha-fetoprotein (AFP) were conducted one month after the operation and at three-month intervals for the first 3 years. After 3 years, routine follow-ups were performed once every 4 months, and then every 6 months after 5 years, using CT scans and AFP assays.

**Statistical analysis**

Categorical variables were compared between the study groups using the Fisher exact test. Continuous variables were expressed as medians with ranges, and compared using the Mann-Whitney U test. The overall survival (OS) and recurrence-free survival (RFS) rates were calculated using the Kaplan–Meier method and compared between the groups using the log-rank test. Potential prognostic factors were identified by univariate analysis using the log-rank test. Independent prognostic factors were evaluated using a Cox proportional-hazards regression model. $P < 0.05$ was considered statistically significant and all statistical analyses were performed using JMP version 14 for Windows (SAS Institute, Cary, NC).

## Results

### Characteristics of the entire study cohort

The clinicopathological features of the patients in the entire cohort analyzed in this study are presented in Table 1. There were 88 stage 0, 750 stage A, and 250 stage B cases in this population. The cohort comprised 892 men (82.0%) and 196 women (18.0%) aged from 18-92 years with a median age of 65 years. A total of 371 patients (34.1%) were positive for hepatitis B surface antigen and 366 cases (33.6%) for hepatitis C virus (HCV) antibody. We categorized 799 patients (73.4%) as no cirrhosis, 272 patients (25.0%) as Child-Pugh A cirrhosis, and 17 (1.6%) as Child-Pugh B cirrhosis. The median ICGR15 was 13.6 % (range, 0.8-94.4 %) and the median AFP was 14.5 ng/ml (range, 0-5986980 ng/ml). The median tumor size in the whole cohort was 4.0 cm (range, 0.5-35.0 cm), with 751 patients (69.0%) having a single tumor and 337 (31.0%) showing multiple tumors. A non-anatomical liver resection was conducted in 315 patients (29.0%), whereas 773 patients (71.0%) underwent an anatomical liver resection. There were 88 (8.1%) stage 0, 485 (44.6%) stage A1, 190 (17.5%) stage A2, 75 (6.9%) stage A3, 166 patients (15.2%) in stage B1, and 84 (7.7%) stage B2 patients in our current series. There were 896 patients (82.4%) showing a well to moderately differentiated HCC and 192 (17.6%) with poor to undifferentiated differentiation. Three hundred and three cases (27.8%) were positive for pathological microvascular invasion. The

median operation time and blood loss were 313 min (range, 88-1335 min) and 420 ml (range, 0-61350 ml), respectively. When we divided the patients into two groups by era of surgery, there were 480 patients (44.1%) in the first period (1991-2005) and 608 patients (55.9%) in the second period (2006-2020).

**Prognostic factors associated with overall and recurrence-free survival in the entire cohort**

In our entire cohort of BCLC Stage 0, A, and B HCC patients, univariate analysis revealed that HCV antibody, Child-Pugh B cirrhosis, ICGR15, AFP, BCLC stage, type of liver resection, histological differentiation, microvascular invasion, and era of surgery were significant prognostic indicators of OS. Multivariate analysis indicated that HCV antibody, Child-Pugh B cirrhosis, ICGR15, AFP, BCLC stage, type of liver resection, microvascular invasion, and era of surgery were independent prognostic indicators of OS (Table 2). Univariate analysis of the whole study population revealed that Child-Pugh B cirrhosis, ICGR15, AFP, BCLC stage, type of liver resection, histological differentiation, and microvascular invasion were significant prognostic indicators of RFS. By multivariate analysis, Child-Pugh B cirrhosis, ICGR15, BCLC stage, type of liver resection, and microvascular invasion were independent prognostic indicators of RFS (Table 2). The BCLC stage thus affected both the OS and RFS outcomes.

**Overall and recurrence-free survival analysis**

The 5-year OS rates for the Stage 0, A1, A2, A3, B1, and B2 cases were 70.4%, 74.2%, 63.8%, 47.7%, 47.5%, and 31.9% (P<0.0001; Figure 1a), and the 5-year RFS rates were 41.9%, 36.5%, 34.8%, 18.3%, 15.3%, and 0.0%, respectively (P<0.0001; Figure 1b). There were significant differences in the OS outcomes between Stage A1 and A2 (P=0.0118), A2 and A3 (P=0.0013), and B1 and B2 (P=0.0050), but not between A3 and B1 (P=0.4742) (Figure 1a). There were also significant differences in the RFS rates between Stage A2 and A3 (P<0.0001) and B1 and B2 (P=0.0047), but not between A1 and A2 (P=0.5940) or between A3 and B1 (P=0.5126) (Figure 1b). No differences were found in either the OS or RFS between Stage A3 and B1.

**Risk factors in patients with a Stage B1 HCC**

Because there were no significant differences found in either the OS or RFS outcomes between StageA3, which is indicated for a liver resection by the BCLC classification system, and Stage B1, we performed subgroup analysis of the prognoses in our Stage B1 study patients. Univariate analysis of these B1 cases revealed that Child-Pugh B cirrhosis was a significant prognostic factor for the OS rate. Multivariate analysis of this subgroup further revealed that Child-Pugh B cirrhosis was an independent prognostic factor

for OS (Table 3). In the same manner, univariate analysis revealed that Child-Pugh B cirrhosis and microvascular invasion were significant prognostic factors for the RFS rate in the Stage B1 HCC patients, with multivariate analysis indicating that both of these variables were independent prognostic factors for the RFS outcome (Table 3).

**Recurrence sites in the BCLC-A3 and -B1 HCC patients**

Because there were no differences between Stage A3 and B1 with respect to either the OS or RFS, we further analyzed the sites of HCC recurrence for both of these HCC classifications. As indicated in Table 4, more patients in the B1 group experienced intrahepatic recurrence, whereas more patients in the A3 group experienced lung recurrence. On the other hand, there were no significant differences between the A3 and B1 groups in terms of other extra-hepatic recurrences at sites such as the bone, lymph node, brain, adrenal gland, or peritoneum.

**Discussion**

The surgical indications for a hepatectomy to treat a single HCC are widely accepted, whereas those for multiple HCCs remain unclear and controversial. The BCLC staging system recommends liver resection only for BCLC-0 and BCLC-A patients, and not for BCLC-B cases. In contrast, Asian guidelines including those from the APASL and the JSH suggest liver

resection as a treatment option for BCLC-B patients [4, 5]. In this present study, we retrospectively assessed the therapeutic value of liver resection for BCLC-B HCC patients, and found that it yields an acceptable surgical outcome for select BCLC-B cases.

In accordance with this staging system, the treatment options for BCLC-B patients in the past have been TACE only, and either TACE or systemic therapy in more recent years [2, 3]. However, a BCLC-B stage comprises a highly heterogeneous population of HCC cases [10], for example containing both Child-Pugh class A and B patients, resulting in an extremely large patient population even from the perspective of a hepatic functional reserve alone. Multiple HCCs beyond the Milan criteria are classified as BCLC stage B and thus involve various sizes and numbers of tumors. Several previous reports have shown that some populations benefit from hepatic resection, even in BCLC stage B patients. Zhong et al. insisted in their prior study that a BCLC-B classification is not a contraindication for hepatic resection from an assessment of the therapeutic value of this surgical approach, and comparing it with TACE among BCLC-B and C patients [11]. Wang et al. have recommended a resection for BCLC-B patients when there is no microvascular invasion [12]. Wada et al. have also contended that a hepatic resection should be considered as a radical treatment for certain patients with multiple BCLC-B HCCs [13]. Our current study findings also suggest that the long-term results of hepatic resection for BCLC-B HCC with three or fewer nodules are equivalent to those for a single large HCC. JSH guidelines also recommend hepatectomy

as a treatment option for HCC cases with three or fewer nodules, but recommend other interventions in cases of four or more nodules [5]. Tsilimigras et al. have reported that the prognosis for a single large HCC was poorer than in other BCLC stage A cases, but was similar to patients presenting with BCLC stage B tumors following a liver resection [14], which is consistent with our current findings. Liver resection for a single large HCC has been associated previously with acceptable long-term outcomes [6, 7, 15]. Taken together therefore, the cumulative evidence to date suggests that a BCLC-B HCC should not be comprehensively regarded as a contraindication for surgery if the tumor number is three or less .

Our current results from multivariate analysis further indicated that only a Child-Pugh B cirrhosis is an independent prognostic factors for OS in patients with a Stage B1 HCC. Liver resection for HCC in a Child-Pugh B cirrhosis background is generally controversial but can be acceptable in select cases, although the prognosis is generally poor. Taura et al. reported that the OS rate following a hepatic resection in Child-Pugh class B cirrhotic patients was poorer than that in both noncirrhotic and Child-Pugh class A cirrhotic patients [16]. Berardi et al. reported that liver resection should be considered for HCC in cases with a Child-Pugh B cirrhosis after careful selection in accordance with the patient characteristics, tumor pattern and liver function [17]. Harimoto et al. stated that a hepatic resection for recurrent HCC and excessive blood loss should be avoided in patients with

Child-Pugh class B cirrhosis [18]. The prognosis of a hepatectomy for Child-Pugh B HCC is not always acceptable. The same theory applies to liver resection for patients with cirrhosis. Taura et al. reported that coexisting cirrhosis is associated with a higher mortality and recurrence rate, and that this limits the efficacy of hepatic resection [16]. These authors insisted that hepatic resection should be the treatment of choice for HCC patients without cirrhosis. Hence, based on the results of our current study and other reports, a liver resection for a BCLC-B HCC should be limited to no cirrhosis or Child-Pugh A cases. Fukami et al. recently reported that a liver resection could offer a good long-term survival outcome for patients with multiple HCCs with up to 3 tumors with a Child-Pugh A grading [19], which is consistent with our present findings. Based on our present observations also, even in BCLC stage B1 cases, the 5-year OS rate for the second surgical period was 60.7% compared to 38.5% in the first period cases (Table 3). Furthermore, our current analyses indicated a 5-year OS rate of 62.3% from a second period hepatectomy in BCLC stage B1/no cirrhosis or Child-Pugh A patients. In contrast, Fukami et al. reported a 5-year OS rate of 41.6% with TACE for HCC patients with up to 3 tumors and a Child-Pugh A grade [19]. Taken together, and since the results from these surgeries have been improving in recent years, a liver resection may be considered even for a BCLC-B HCC if the tumor number is three or less, especially in patients with a no cirrhosis or Child-Pugh A classification.

Our present observations have also indicated that patients with a single large HCC

had similar long-term results to those with multiple HCCs of three or less. In 2011, the original BCLC staging system was updated to define a single large HCC (≥ 5 cm) as BCLC stage A rather than stage B [20]. The current BCLC staging system also follows that definition [2, 3]. Among several factors, the tumor size has been reported to correlate with a poor prognosis in HCC patients [21, 22]. Jung et al. have suggested that a single large HCC should be classified as BCLC stage B, rather than stage A [23]. In our present analyses, the long-term results after hepatic resection were found to be similar for the stage A3 and B1 patients. However, in terms of recurrence, pulmonary recurrence was more common in the stage A3 cases, while hepatic recurrence was more common in our stage B1 patients. Hence, stage A3 and B1 HCCs cannot be regarded as the same group. However, many previous reports have suggested that liver resection should be indicated for a single HCC even if it is large in size [6, 7]. In addition, our present study found that the results of a hepatectomy for multiple HCCs in select patients are comparable to those for a single large HCC treated in this way. Hence, a designation of BCLC stage B should not be considered an *a priori* contraindication for a liver resection.

The treatment of HCC has evolved dramatically and has diversified in recent years. In particular, the development of systemic therapy has changed the treatment systems available for HCC. In the treatment of BCLC-B HCCs, only TACE was applied previously [3]. However, both TACE and systemic therapy can now be indicated for this grade of HCC in

accordance with the revised BCLC staging system [2]. In the HCC field, the possibility of conversion surgery has recently been explored with the development of systemic therapy, although the preoperative treatments for HCC have not yet been standardized [24-27]. Currently, the mainstays of the systemic therapies for HCC are atezolizumab plus bevacizumab, sorafenib, and lenvatinib. Atezolizumab plus bevacizumab has now become the first-line systemic treatment for unresectable HCC, but its impact on conversion surgery is still unknown. However, knowledge of the impacts of lenvatinib has been accumulating with regard to conversion surgery for HCC. Shindoh et al. recently reported clinical data from conversion surgeries after lenvatinib treatment for HCCs including BCLC stages A-C [27]. These authors concluded that conversion surgery after lenvatinib treatment may offer a significant survival benefit in select patients as long as an R0 resection is achieved. In the future therefore, conversion surgery may offer a better prognosis for patients with multiple HCCs, and liver resection may be indicated even for cases of four or more nodules with preoperative treatment.

Our present study had some notable limitations including its retrospective nature and examination of patients from a single center. Hence, a potential bias may have existed in relation to the enrolled cohort. In addition, this study lacked a control group that received TACE or systemic therapy and we could not make definitive conclusions regarding the superiority of different treatment approaches for patients with multiple HCCs. Furthermore,

this study included only patients who were eligible for hepatic resection. Since this study did not examine total patient population, including those treated with therapies other than hepatic resection, especially for stage B1 and B2 cases, patients who underwent liver resection for multiple HCCs is a highly select population. Hence, a selection bias also existed when liver resection was chosen instead of TACE or systemic therapy. However, while the indications for HCC surgery differ between Europe, the US, and Asia, our present investigation was a valuable examination of Japanese liver resection cases from the perspective of a Western staging system.

In conclusion, the long-term results of a hepatectomy for multiple HCCs are equivalent to those for a single HCC if the tumor number is three or less, and a good prognosis can be expected for patients with a no cirrhosis or Child-Pugh A grading. Hence, hepatic resection should be considered for patients with multiple HCCs if they have no cirrhosis or a good functional liver reserve and there are three or fewer tumors.

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**Figure legend**

**Figure 1.** (a) Significant differences in overall survival between the Stage A1 and A2 (P=0.0118), A2 andA3 (P=0.0013), and B1 and B2 (P=0.0050) HCC patients. There were no significant differences between the Stage 0 and A1 (P=0.8679) or between the Stage A3 and B1 (P=0.4742) cases. (b) Significant differences in recurrence-free survival between StageA2 and A3 (P<0.0001) and between Stage B1 and B2 (P=0.0047). There were no significant differences between Stage 0 andA1 (P=0.2150), A1 and A2 (P=0.5940), or A3 and B1 (P=0.5129).

**Table 1 Clinicopathological characteristics of the entire cohort**

| Variables | | Value |
|---|---|---|
| Age | | |
| | | 65 (18-92) |
| Gender | | |
| | Female | 196 (18.0%) |
| | Male | 892 (82.0%) |
| HBs antigen | | |
| | Negative | 717 (65.9%) |
| | Positive | 371 (34.1%) |
| HCV antibody | | |
| | Negative | 722 (66.4%) |
| | Positive | 366 (33.6%) |
| Liver cirrhosis and Child Pugh classification | | |
| | No cirrhosis | 799 (73.4%) |
| | Child-Pugh A cirrhosis | 272 (25.0%) |
| | Child-Pugh B cirrhosis | 17 (1.6%) |
| ICG R15 (%) | | |
| | | 13.6 (0.8-94.4) |
| AFP(ng/ml) | | |
| | | 14.5 (0-5986980) |
| Tumor size (cm) | | |
| | | 4.0 (0.5-35.0) |
| Tumor number | | |
| | Single | 751 (69.0%) |
| | Multiple | 337 (31.0%) |
| Liver resection | | |
| | Non-anatomical | 315 (29.0%) |
| | Anatomical | 773 (71.0%) |
| BCLC stage | | |
| | 0 | 88 (8.1%) |
| | A1 | 485 (44.6%) |
| | A2 | 190 (17.5%) |
| | A3 | 75 (6.9%) |
| | B1 | 166 (15.2%) |
| | B2 | 84 (7.7%) |
| Differentiation | | |
| | Well to moderate | 896 (82.4%) |
| | Poor to undifferentiated | 192 (17.6%) |
| Microvascular invasion | | |
| | Absence | 785 (72.2%) |
| | Presence | 303 (27.8%) |
| Operation time (min) | | |
| | | 313 (88-1335) |
| Blood loss (ml) | | |
| | | 420 (0-61350) |
| Era of surgery | | |
| | First period (1991-2005) | 480 (44.1%) |
| | Second period (2006-2020) | 608 (55.9%) |

Abbreviations: HBs antigen, hepatitis B surface antigen; HCV antibody, hepatitis C virus antibody; ICGR15, indocyanine green retention rate at 15 minutes; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer

Continuous variables are expressed as a median value (range)

**Table 2 Univariate and multivariate analyses of the prognostic factors in the entire cohort**

| | | Univariate analysis | | | |
|---|---|---|---|---|---|
| | | Overall survival | | Recurrence-free survival | |
| Variable | n | 5-years (%) | P value | 5-years (%) | P value |
| Age | | | 0.4523 | | 0.4708 |
| <60 | 337 | 62.5±2.7 | | 29.3±2.5 | |
| ≥60 | 751 | 63.4±2.1 | | 29.6±1.9 | |
| Gender | | | 0.4618 | | 0.9531 |
| Female | 196 | 62.0±4.0 | | 30.1±3.6 | |
| Male | 892 | 63.6±1.8 | | 29.5±1.7 | |
| HBs antigen | | | 0.3490 | | 0.0606 |
| Negative | 717 | 62.5±2.1 | | 30.2±1.9 | |
| Positive | 371 | 64.2±2.7 | | 28.1±2.4 | |
| HCV antibody | | | 0.0060 | | 0.3195 |
| Negative | 722 | 67.2±2.0 | | 31.8±1.9 | |
| Positive | 366 | 56.3±2.9 | | 25.7±2.5 | |
| Liver cirrhosis and Child Pugh classification | | | <0.0001 | | <0.0001 |
| No cirrhosis | 799 | 67.4±1.9 | | 34.0±1.9 | |
| Child-Pugh A cirrhosis | 272 | 54.6±3.2 | | 19.1±2.5 | |
| Child-Pugh B cirrhosis | 17 | 38.5±13.4 | | 12.6±8.3 | |
| ICG R15 (%) | | | 0.0017 | | 0.0003 |
| <15 | 625 | 66.0±2.1 | | 33.9±2.1 | |
| ≥15 | 463 | 59.7±2.6 | | 24.0±2.2 | |
| AFP(ng/ml) | | | 0.0002 | | 0.0141 |
| <400 | 869 | 66.9±1.8 | | 30.3±1.7 | |
| ≥400 | 219 | 49.2±3.7 | | 26.3±3.1 | |
| BCLC stage | | | <0.0001 | | <0.0001 |
| 0 | 88 | 70.4±5.7 | | 41.9±5.9 | |
| A1 | 485 | 74.2±2.2 | | 36.5±2.4 | |
| A2 | 190 | 63.8±3.9 | | 34.8±3.7 | |
| A3 | 75 | 47.7±7.0 | | 18.3±5.0 | |
| B1 | 166 | 47.5±4.5 | | 15.3±3.1 | |
| B2 | 84 | 31.9±5.9 | | 0.0±0.0 | |
| Liver resection | | | 0.0039 | | 0.0068 |
| Non-anatomical | 315 | 54.5±3.2 | | 22.0±2.6 | |
| Anatomical | 773 | 67.2±1.9 | | 32.8±1.8 | |
| Differentiation | | | 0.0099 | | 0.0061 |
| Well to moderate | 896 | 65.1±1.8 | | 31.1±1.7 | |
| Poor to undifferentiated | 192 | 55.3±4.1 | | 22.7±3.4 | |
| Microvascular invasion | | | <0.0001 | | <0.0001 |
| Absence | 785 | 70.2±1.8 | | 33.7±1.8 | |
| Presence | 303 | 44.3±3.4 | | 19.2±2.5 | |
| Era of surgery | | | 0.0015 | | 0.9584 |
| First period (1991-2005) | 480 | 59.3±2.3 | | 28.8±2.1 | |
| Second period (2006-2020) | 608 | 68.5±2.3 | | 30.7±2.2 | |

| | Multivariate analysis | | |
|---|---|---|---|
| | Overall survival | | |
| | HR | 95% CI | P value |
| HCV antibody | 1.357 | 1.102-1.670 | 0.0039 |
| Child-Pugh B cirrhosis vs No cirrhosis | 2.564 | 1.378-4.773 | 0.0030 |
| Child-Pugh B cirrhosis vs Child-Pugh A cirrhosis | 1.606 | 0.864-2.984 | 0.1335 |
| ICG R15 >15 (%) | 1.285 | 1.044-1.583 | 0.0177 |
| AFP >400 (ng/ml) | 1.264 | 1.005-1.591 | 0.0449 |
| BCLC stage A1 vs 0 | 1.000 | 0.678-1.475 | 0.9979 |
| A2 vs 0 | 1.554 | 1.010-2.393 | 0.0449 |
| A3 vs 0 | 3.533 | 2.109-5.919 | <0.0001 |
| B1 vs 0 | 2.249 | 1.462-3.459 | 0.0002 |
| B2 vs 0 | 4.001 | 2.521-6.349 | <0.0001 |
| Non-anatomical resection | 1.431 | 1.128-1.815 | 0.0031 |
| Microvascular invasion | 1.904 | 1.533-2.365 | <0.0001 |
| Era of surgery: First period (1991-2005) | 1.298 | 1.056-1.595 | 0.0129 |

| | Recurrence-free survival | | |
|---|---|---|---|
| | HR | 95% CI | P value |
| Child-Pugh B cirrhosis vs No cirrhosis | 2.502 | 1.477-4.239 | 0.0006 |
| Child-Pugh B cirrhosis vs Child-Pugh A cirrhosis | 1.792 | 1.058-3.037 | 0.0300 |
| ICG R15 >15 (%) | 1.267 | 1.082-1.482 | 0.0032 |
| BCLC stage A1 vs 0 | 1.195 | 0.883-1.615 | 0.2436 |
| A2 vs 0 | 1.331 | 0.945-1.874 | 0.1013 |
| A3 vs 0 | 2.889 | 1.936-4.310 | <0.0001 |
| B1 vs 0 | 2.373 | 1.696-3.321 | <0.0001 |
| B2 vs 0 | 3.970 | 2.713-5.810 | <0.0001 |
| Non-anatomical resection | 1.312 | 1.095-1.572 | 0.0031 |
| Microvascular invasion | 1.713 | 1.443-2.034 | <0.0001 |

Abbreviations: HBs antigen, hepatitis B surface antigen; HCV antibody, hepatitis C virus antibody; ICGR15, indocyanine green retention rate at 15 minutes; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HR, hazard ratio; CI, confidence interval

**Table 3 Univariate and multivariate analyses of prognostic factors in the BCLC-B1 cohort**

| | | Univariate analysis | | | |
|---|---|---|---|---|---|
| | | Overall survival | | Recurrence-free survival | |
| Variable | n | 5-years (%) | P value | 5-years (%) | P value |
| Age | | | 0.0994 | | 0.2794 |
| <60 | 56 | 39.3±7.1 | | 11.6±4.4 | |
| ≥60 | 110 | 52.1±5.8 | | 17.1±4.3 | |
| Gender | | | 0.4994 | | 0.5395 |
| Female | 22 | 55.0±13.6 | | 7.6±6.7 | |
| Male | 144 | 46.5±4.8 | | 16.5±3.4 | |
| HBs antigen | | | 0.2182 | | 0.1323 |
| Negative | 97 | 50.5±6.1 | | 16.0±4.4 | |
| Positive | 69 | 43.1±6.8 | | 13.6±4.4 | |
| HCV antibody | | | 0.0873 | | 0.5174 |
| Negative | 115 | 54.9±5.5 | | 19.3±4.0 | |
| Positive | 51 | 32.3±7.6 | | 8.4±4.3 | |
| Liver cirrhosis and Child Pugh classification | | | <0.0001 | | <0.0001 |
| No cirrhosis | 123 | 48.8±5.4 | | 15.6±3.9 | |
| Child-Pugh A cirrhosis | 39 | 47.0±9.0 | | 13.6±5.6 | |
| Child-Pugh B cirrhosis | 4 | 0.0±0.0 | | 0.0±0.0 | |
| ICG R15 (%) | | | 0.7358 | | 0.5074 |
| <15 | 102 | 48.6±5.8 | | 15.6±4.1 | |
| ≥15 | 64 | 46.7±7.3 | | 15.8±4.9 | |
| AFP(ng/ml) | | | 0.7453 | | 0.7080 |
| <400 | 116 | 48.6±5.7 | | 11.4±3.7 | |
| ≥400 | 50 | 44.4±7.6 | | 20.0±5.6 | |
| Liver resection | | | 0.1052 | | 0.5495 |
| Non-anatomical | 34 | 34.7±9.6 | | 12.9±6.0 | |
| Anatomical | 132 | 50.8±5.1 | | 15.5±3.7 | |
| Differentiation | | | 0.8201 | | 0.2282 |
| Well to moderate | 137 | 48.1±5.0 | | 16.5±3.6 | |
| Poor to undifferentiated | 29 | 45.2±11.0 | | 9.6±5.9 | |
| Microvascular invasion | | | 0.2097 | | 0.0250 |
| Absence | 99 | 50.2±5.7 | | 17.3±4.9 | |
| Presence | 67 | 43.4±7.7 | | 14.8±4.0 | |
| Era of surgery | | | 0.0597 | | 0.8399 |
| First period (1991-2005) | 72 | 38.5±5.9 | | 15.5±4.3 | |
| Second period (2006-2020) | 94 | 60.7±6.4 | | 13.7±5.4 | |

| Multivariate analysis | | | |
|---|---|---|---|
| Overall survival | | | |
| | HR | 95% CI | P value |
| Child-Pugh B cirrhosis vs No cirrhosis | 10.082 | 2.941-34.566 | 0.0002 |
| Child-Pugh B cirrhosis vs Child-Pugh A cirrhosis | 7.448 | 2.096-26.469 | 0.0019 |
| Recurrence-free survival | | | |
| | HR | 95% CI | P value |
| Child-Pugh B cirrhosis vs No cirrhosis | 12.230 | 3.568-41.917 | <0.0001 |
| Child-Pugh B cirrhosis vs Child-Pugh A cirrhosis | 10.143 | 2.891-35.588 | 0.0003 |
| Microvascular invasion | 1.561 | 1.094-2.226 | 0.0140 |

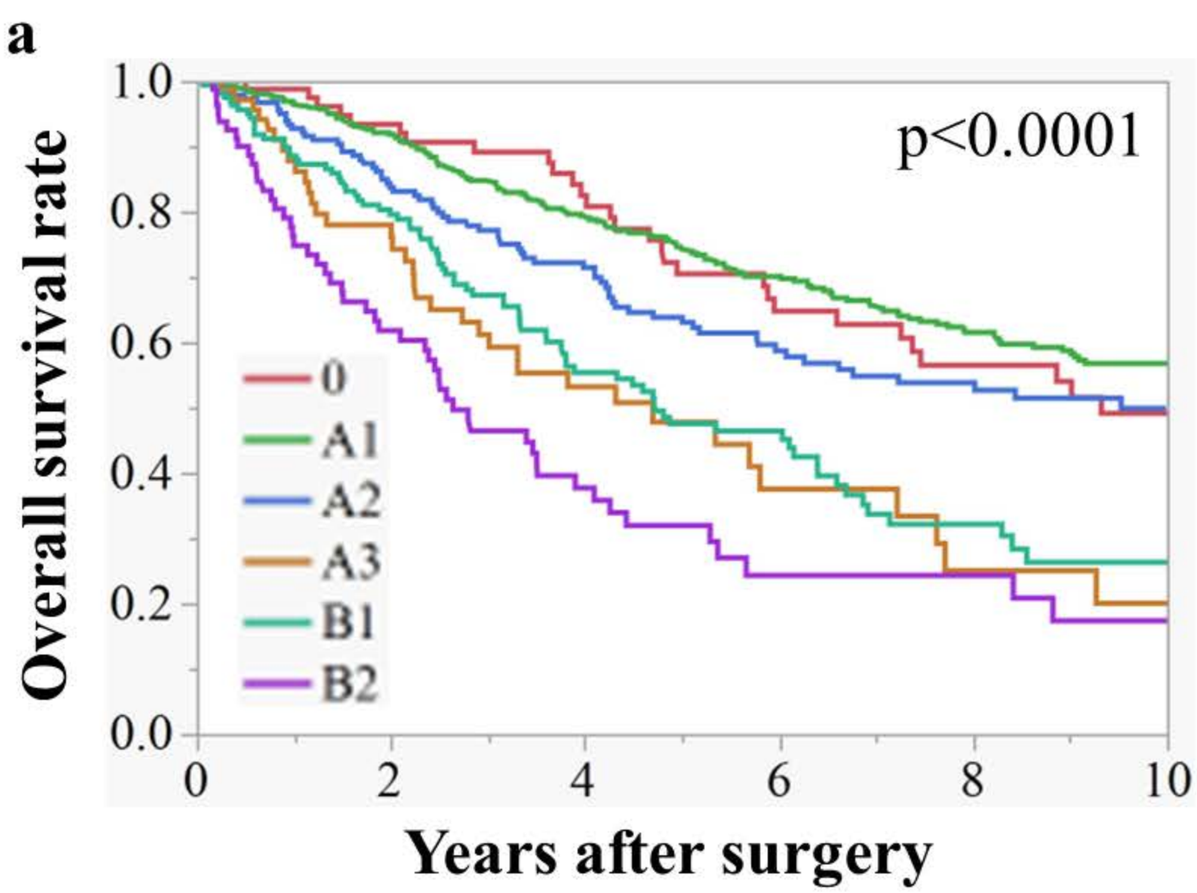
Abbreviations: HBs antigen, hepatitis B surface antigen; HCV antibody, hepatitis C virus antibody; ICGR15, indocyanine green retention rate at 15 minutes; AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Cancer; HR, hazard ratio; CI, confidence interval

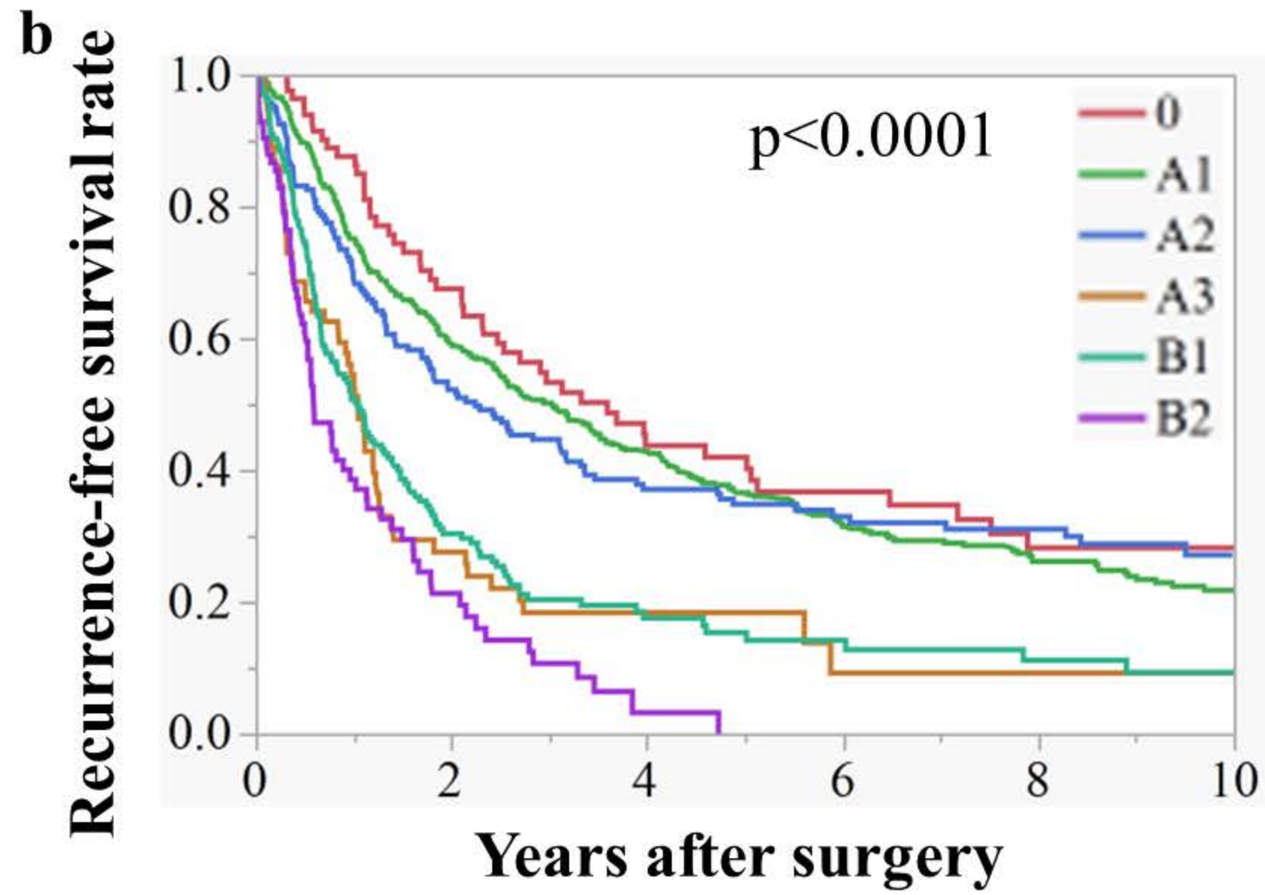
**Table 4 Recurrence sites of BCLC-A3 and BCLC-B1 HCC**

| Recurrence site | BCLC-A3 HCC (n = 75) | BCLC-B1 HCC (n = 166) | p value |
|---|---|---|---|
| Liver | 33 (44.0%) | 104 (62.7%) | 0.0078 |
| Lung | 25 (33.3%) | 31 (18.7%) | 0.0204 |
| Bone | 11 (14.7%) | 21 (12.7%) | 0.6847 |
| Lymph node | 7 (9.3%) | 15 (9.0%) | 1.0000 |
| Brain | 3 (4.0%) | 3 (1.8%) | 0.3787 |
| Adrenal gland | 5 (6.7%) | 9 (5.4%) | 0.7681 |
| Peritoneum | 2 (2.7%) | 3 (1.8%) | 0.6479 |

Abbreviations: BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma

**Figure. 1**




| | | |
|---|---|---|
| Stage 0 | vs StageA1 | (p=0.8679) |
| StageA1 | vs StageA2 | (p=0.0118) |
| StageA2 | vs StageA3 | (p=0.0013) |
| StageA3 | vs StageB1 | (p=0.4742) |
| StageB1 | vs StageB2 | (p=0.0050) |

| | | |
|---|---|---|
| Stage 0 | vs StageA1 | (p=0.2150) |
| StageA1 | vs StageA2 | (p=0.5940) |
| StageA2 | vs StageA3 | (p<0.0001) |
| StageA3 | vs StageB1 | (p=0.5126) |
| StageB1 | vs StageB2 | (p=0.0047) |