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Title	Hepatectomy is Beneficial in Select Patients with Multiple Hepatocellular Carcinomas
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Citation	Annals of surgical oncology, 29(13), 8436-8445 https://doi.org/10.1245/s10434-022-12495-z
Issue Date	2022-12-01
Doc URL	http://hdl.handle.net/2115/90946
Rights	This version of the article has been accepted for publication, after peer review (when applicable) and is subject to Springer Nature's AM terms of use, but is not the Version of Record and does not reflect post-acceptance improvements, or any corrections. The Version of Record is available online at: http://dx.doi.org/10.1245/s10434-022-12495-z
Type	article (author version)
File Information	Ann Surg Oncol 29 8436-8445.pdf

Hepatectomy is Beneficial in Select Patients with Multiple Hepatocellular Carcinomas

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Running head: Surgery for multiple hepatocellular carcinoma

Conflicts of interest: The authors declare no conflicts of interest in relation to this study.

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 ($\geq$ 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

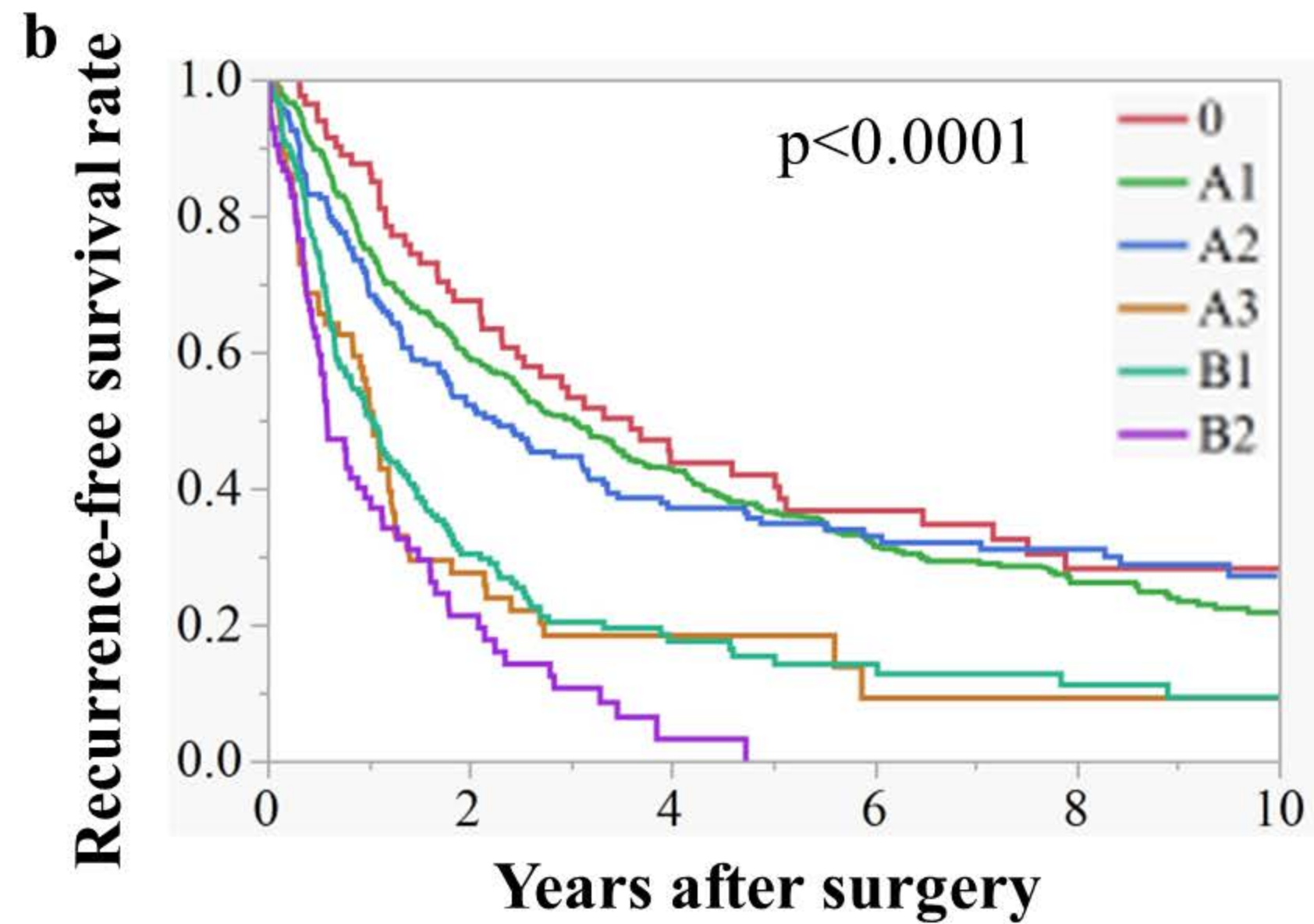**Table 4 Recurrence sites of BCLC-A3 and BCLC-B1 HCC**

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

a

Overall survival rate / Years after surgery

p<0.0001

Legend: 0, A1, A2, A3, B1, B2
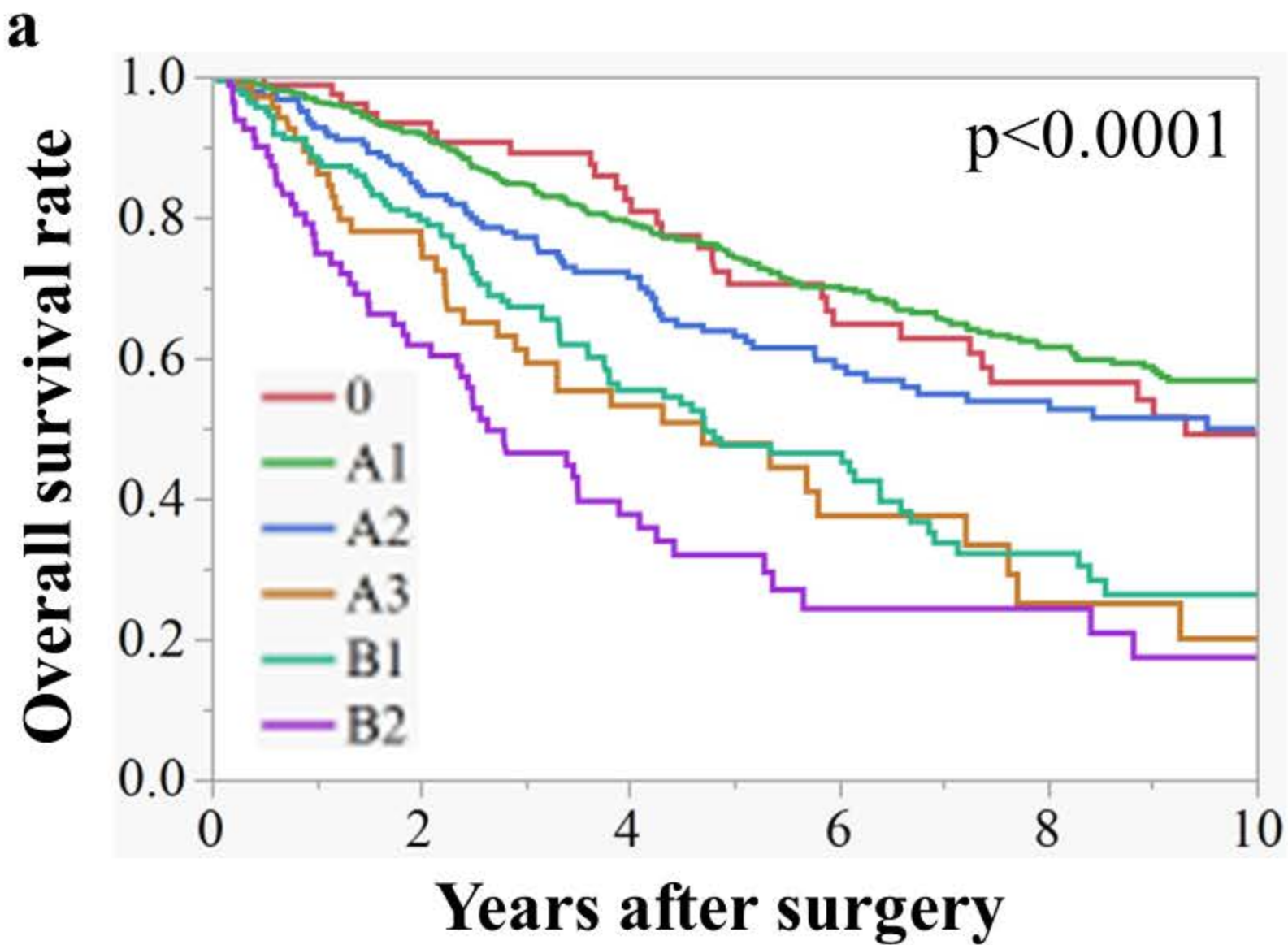
Stage 0   vs StageA1   (p=0.8679)
StageA1 vs StageA2   (p=0.0118)
StageA2 vs StageA3   (p=0.0013)
StageA3 vs StageB1   (p=0.4742)
StageB1 vs StageB2   (p=0.0050)

b

Recurrence-free survival rate / Years after surgery

p<0.0001

Legend: 0, A1, A2, A3, B1, B2

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)