




Preventing Recurrence of Hepatocellular Carcinoma After Curative Hepatectomy With Active Hexose-correlated Compound Derived From *Lentinula edodes* Mycelia

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Abstract

Purpose: Active hexose-correlated compound (AHCC), a standardized extract of cultured *Lentinula edodes* mycelia, exerts antitumor effects through anti-inflammatory and immune-modulatory functions. Adjuvant therapy for patients with hepatocellular carcinoma (HCC) who have undergone curative hepatectomy has not been established. The purpose of this study was to evaluate the efficacy and safety of AHCC as adjuvant therapy in patients with advanced HCC after curative hepatectomy. **Patients and methods:** The study design was single-armed, non-randomized, open (no one was blinded), and uncontrolled. Patients with HCC who underwent curative hepatectomy were treated with AHCC (1 g) 3 times daily orally for 2 years. The inclusion criteria were HCC diagnosed preoperatively as stages A and B of the Barcelona clinic liver cancer (BCLC) classification and alpha-fetoprotein \times protein induced by vitamin K absence or antagonist II (PIVKA-II) $\geq 10^5$ for stage A. **Results:** A total of 29 patients were treated with AHCC, of which 25 (4 patients discontinued) were followed up. The 2-year recurrence-free survival rate after resection was 48% for those without discontinuations and 55.2% for all patients with a history of treatment. Serum albumin levels decreased to a minimum in the first postoperative month and gradually recovered to the preoperative level at 6 months. Almost no change in lymphocyte percentage was observed during follow-up. Inflammation-based prognostic scores were maintained at favorable levels after hepatectomy. Toxicity and adverse events were not observed in any patient. **Conclusion:** AHCC may be safe and effective in preventing HCC recurrence after curative hepatectomy, and further randomized trials of AHCC for its use in this setting are warranted.

This clinical trial was registered in UMIN Clinical Trials Registry (ID UMIN000024396).

Keywords

AHCC, hepatocellular carcinoma, hepatectomy, recurrence, adjuvant

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Introduction

Liver cancer is the third leading cause of cancer-related deaths worldwide.¹ Hepatocellular carcinoma (HCC) has a poor prognosis and accounts for 70% to 85% of primary liver cancers.² Hepatectomy for HCC yields the highest local control of all local treatments, with a good survival rate.³ However, according to the Barcelona clinic liver cancer (BCLC) staging classification, hepatectomy is contraindicated in intermediate-stage patients (stage B HCC) and transarterial chemoembolization (TACE) or systemic

therapy (Atezolizumab plus bevacizumab) are suggested.⁴ In contrast to the BCLC staging guidelines, hepatectomy is suggested in some patients with stage B HCC according to a Japanese evidence-based treatment algorithm⁵ and

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clinical practice guidelines for HCC proposed by the Japan Society of Hepatology (JSH algorithm),⁶ with acceptable prognoses.^{7,8} However, hepatectomy is associated with a high risk of HCC recurrence.⁹ The use of adjuvant therapy for patients with HCC who have undergone curative hepatectomy has not been established, although new therapies, such as molecular targeted therapy and immune check-point inhibition, are available.^{10,11}

Active hexose-correlated compound (AHCC), produced by Amino Up Co., Ltd. (Sapporo, Japan), is a standardized extract of cultured *Lentinula edodes* (Shiitake) mycelia obtained through the liquid culture of shiitake mycelia.¹² AHCC contains various nutrients including oligosaccharides, amino acids, and minerals. The effect of AHCC on the immune system for malignancy by natural killer (NK) and T cell, its usefulness in clinical cancer therapy¹³⁻¹⁵ and its anti-inflammatory and anti-oxidant effects¹⁶⁻¹⁸ have been reported. Only 1 study reported that the intake of AHCC improved the prognosis for patients with HCC who underwent curative hepatectomy.¹⁹ However, in this study, patients in early to advanced stages were included, and the host-inflammatory response was not analyzed, although this response has been previously reported to be associated with cancer progression and patient survival.²⁰

The purpose of this study was the preliminary assessment of the efficacy, safety, and outcome of AHCC as adjuvant therapy in patients with advanced HCC after curative hepatectomy and the evaluation of the host-inflammatory response.

Methods

Study Design

The study design was single-armed, non-randomized, open (no one was blinded), and uncontrolled. The study period was from November 19, 2016 to March 31, 2021. The patients who had undergone curative hepatectomy at Hokkaido University Hospital during the same period were recruited by the physician co-investigators of the study based on their written informed consent. Patients with curative hepatectomy were administered 1 g AHCC orally, 3 times daily for 2 years. We used commercially available AHCC that was provided to us multiple times. AHCC was stored at room temperature (23°C) and used before its expiry date based on Food Labeling Guideline in Japan. Inclusion criteria for this study were: HCC diagnosed using computed tomography (CT) and/or magnetic resonance imaging (MRI) within stages A and B of BCLC classification; without pretreatment for HCC; alpha-fetoprotein (AFP) × protein induced by vitamin K absence or antagonist II (PIVKA-II) $\geq 10^5$ for stage A; without distant metastasis and macroscopic tumor thrombus; age 20 to 85; ECOG

performance status 0 to 2; Child–Pugh score ≤ 7 ; functional reserves of bone marrow, liver, and kidney; WBC $\geq 2000/\text{mm}^3$ and $\leq 10\,000/\text{mm}^3$; platelets $\geq 50\,000/\text{mm}^3$; Hb ≥ 8.0 g/dL; total bilirubin ≤ 2.0 mg/dL; prothrombin time activity $\geq 50\%$; creatinine ≤ 1.5 mg/dL; BUN ≤ 35 mg/dL; and acceptance of informed consent. Exclusion criteria were: other cancers, severe cardiac and/or pulmonary failure, renal failure contraindication of enhanced CT and/or MRI, mental illness, pregnancy, previous intake of AHCC, and contraindications as decided by the physician co-investigators of the study. Clinical, laboratory, surgical, and pathological data of enrolled patients were prospectively collected and retrospectively analyzed.

Toxicity was assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) ver. 4.0. This assessment was performed once every 3 months to 2 years along with the physical examination and blood tests after hepatectomy by a physician coinvestigator in an outpatient setting. The drug intake was delayed if toxicity \geq grade 3 was observed and stopped if the patients no longer met the eligibility criteria or if tumors recurred.

All analyses in this study were performed in accordance with the ethical guidelines of Hokkaido University Hospital and according to the Declaration of Helsinki. This study was approved by the Institutional Review Board of Hokkaido University (E016-0100) (November 9, 2016).

Hepatectomy

We used our algorithm, which incorporates indocyanine green retention rate at 15 minutes (ICGR15) and remnant liver volume, to determine the optimal operative procedure, as described.²¹ Anatomical resection is defined as complete anatomical removal of lesion(s) based on Couinaud's classification (segmentectomy, sectionectomy, and hemihepatectomy or extended hemihepatectomy) in patients with sufficient functional reserve. Non-anatomical partial but complete resection was achieved in all patients. R0 resections were performed in all patients, and all resection surfaces were histologically free of HCC.

HCC Recurrence

In the first postoperative month after hepatectomy, patients underwent follow-up evaluations comprising liver function tests, measurements of AFP and PIVKA-II, ultrasonography, and dynamic CT. In the first postoperative month after hepatectomy, the same follow-up study was performed once every 3 months to 2 years after hepatectomy. If recurrence was suspected, CT and MRI were performed; if necessary, CT angiography and bone scintigraphy were performed. This enabled precise determination of the site, number, size, and extent of invasion of recurrent lesions.

Statistical Analysis

Overall survival (OS) and disease-free survival (DFS) rates were calculated using the Kaplan–Meier method. Potential prognostic factors were identified through a univariate analysis using the log-rank test. Independent prognostic factors were evaluated using a multivariable logistic regression analysis. Statistical significance was set at $P < .05$. Statistical analyses were performed using the JMP software (version 14 for Windows; SAS Institute, Cary, NC, USA).

Results

A total of 31 patients were included in this study, of which 29 were treated with AHCC. Two patients were not treated with AHCC because of procedural inconvenience. Due to other malignant diseases, such as malignant lymphoma, prostate cancer, and tongue cancer, the administration of AHCC was stopped in 3 cases after 2.4, 13.4, and 16.3 months. In 1 case, the administration of AHCC was stopped because of the patient's refusal after 2 weeks. The mean period of administration of these 4 patients was 8.2 months. A prognostic analysis was performed for 25 patients and safety analysis for 29 patients who were treated with AHCC. Table 1 shows the data of the 29 treated patients, with the mean age of 68 (36–84). The number of males and females was 27 and 2, respectively. 11. The average length of follow-up of the patients in the study was 22 months.

Adverse Effects of AHCC

Fever of 38.0°C to 39.0°C for 4 days was observed in 1 case and this patient recovered with symptomatic treatment. This fever occurred 2 weeks after the operation and was related to the operation and not to the side effects of AHCC. No AHCC-related toxicity of \geq grade 3 or adverse events were observed in all 29 patients.

Recurrence and Death

Recurrence occurred in 13 patients (13/25, 52%). Recurrent sites are shown in Figure 1. Remnant liver with multiple nodules was present in 3 cases, with solitary nodules in 6 cases, and with extrahepatic metastasis (lung and bone) in 1 case. Three cases with only distant metastasis without liver recurrence were observed, and the site of recurrence was the lymph node in 1 case and the lung in 2 cases (solitary and multiple). The mean duration from hepatectomy to recurrence was 9.5 months.

The recurrence-free survival rate at 2 years in 25 patients (excluding 4 cases who discontinued) was 48% (Figure 2a), whereas that of all 29 treated cases was 55.2% (Figure 2b). Death occurred in 1 patient with recurrence in the hilar region of the liver and periaortic lymph nodes of the abdomen, followed by obstructive jaundice with increasing size,

Table 1. Patient Characteristics.

Variable	(n) or (mean)	Range
Age (year)	68	36-84
Sex		
male:female	27:2	
Hepatic virus status		
HBV	10	
HCV	4	
NBNC	15	
Albumin (g/dL)	4.2	3.6-4.8
Total bilirubin (mg/dL)	0.6	0.3-0.9
ICGR15 (%)	10.8	1.4-23.5
NLR	3	0.8-12.7
SII	625	150.7-3242.1
PNI	50	39.7-58.7
Size (mm)	79.4	32-170
Number		
Solitary	21	
Multiple	8	
Stage		
II	18	
III	10	
Iva	1	
BCLC stage		
A	1	
B	28	
AFP (ng/mL)	26676	1.8-471 728
PIVKA-II (mAU/mL)	9632.4	17-140 350
AP-factor		
Low	16	
High	13	
Child–Pugh		
A	29	
Differentiation		
Well	1	
Moderate	16	
Poor	12	
Vascular invasion		
vp+	2	
vp-	22	
vv+	10	
vv-	19	
Fibrosis ²²		
F0	5	
F1	9	
F2	12	
F3	3	

Abbreviations: HBV, hepatitis B virus surface antigen-positive, hepatitis C virus antibody-negative; HCV, hepatitis B virus surface antigen negative, hepatitis C virus antibody-positive; NBNC, hepatitis B virus surface antigen negative, hepatitis C virus antibody-negative; ICGR15, indocyanine green retention rate at 15 minutes; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; PNI, prognostic nutritional index; BCLC stage, Barcelona clinic liver cancer staging classification; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist II; AP-factor, AFP \times PIVKA-II; vp, microscopic tumor thrombus in the portal vein; vv, microscopic tumor thrombus in the hepatic vein; F0, absence of fibrosis; F1, portal fibrosis with no septa; F2, portal fibrosis with infrequent septa; F3, numerous septa but no cirrhosis.

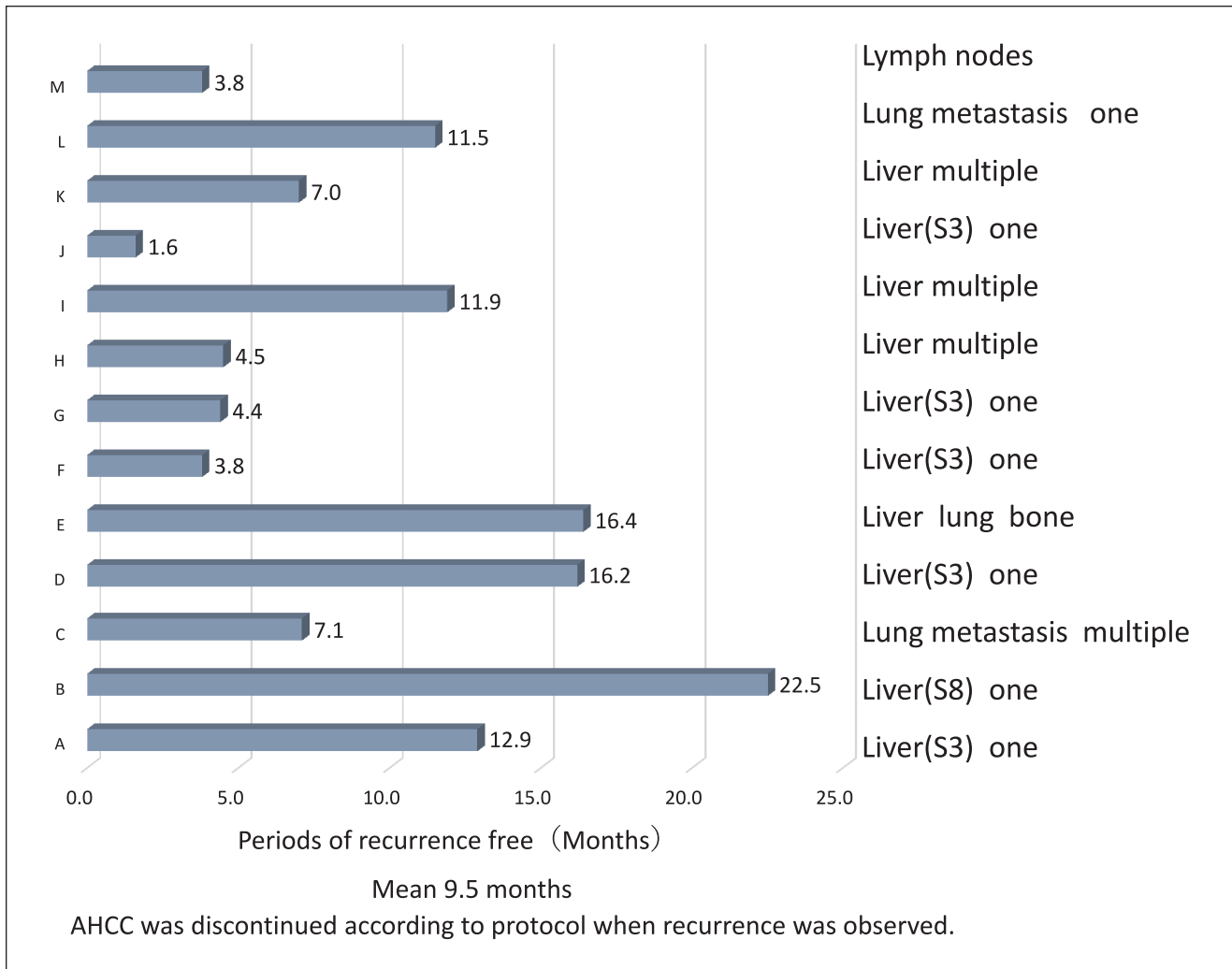


Figure 1. Recurrence occurred in 13/15 (52%) patients. Sites of recurrence included remnant liver with multiple nodules in 3 cases, solitary nodules in 6 cases, and extrahepatic metastasis (lung and bone) in 1 case. Extrahepatic metastasis was observed only in the lymph nodes and lungs (multiple and solitary). The mean duration from hepatectomy to recurrence was 9.5 months.

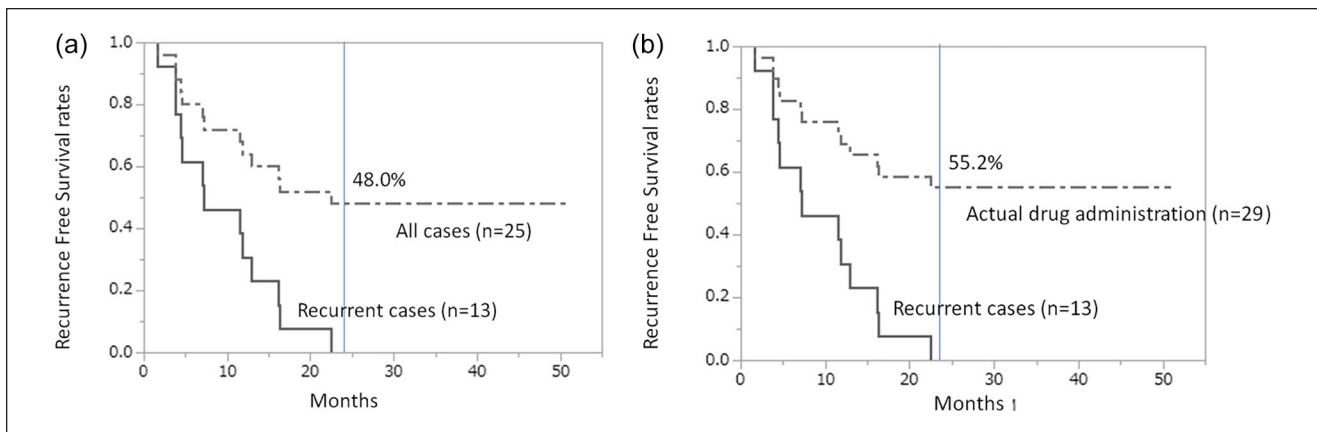


Figure 2. Kaplan–Meier curves for recurrence-free survival. (A) Recurrence-free survival rate at 2 years in 25 patients (excluding 4 cases who discontinued) was 48%. (B) Recurrence-free survival rate at 2 years in 29 treated cases was 55.2%.

liver failure, and death. In this patient, AHCC was discontinued according to the protocol when lymph node recurrence was observed.

For patients with recurrence within 2 years, a significant increase in preoperative total bilirubin level ($P=.01$), AP-factor value ($P=.027$), and hepatic vein invasion ($P=.0148$) was observed compared with that in patients without recurrence (Table 2).

The logistic regression analysis of recurrence at 2 years after hepatectomy revealed that hepatic vein invasion was an independent prognostic factor (Table 3).

Change of Clinical Parameters and Inflammation-based Parameters

In both recurrence (+) and no recurrence (−) groups, serum albumin levels decreased to a minimum in the first postoperative month. Serum albumin levels in the first postoperative month in the recurrence (+) group were lower than those in the recurrence (−) group, although the difference was not significant. At postoperative 6 months, levels in both groups gradually recovered to preoperative levels (Figure 3a). Almost no change in lymphocyte percentage in either group was observed during the follow-up (Figure 3b).

Regarding inflammation-based scores, changes in the neutrophil-to-lymphocyte ratio (NLR) were not different between the groups, and levels of NLR were maintained at <3.5 which were the cut-off points given in the report by Wang et al²³ (Figure 4a). Prognostic nutritional index (PNI) score = albumin (g/dL) + $0.005 \times$ total lymphocyte count (mm^3) decreased to a minimum in the first postoperative month and gradually recovered, although the minimum levels were not <46 which were also the cut-off points given in the report by Wang et al²³ (Figure 4b). Systemic inflammation index (SII) score = Platelet ($\times 10^9/\text{L}$) \times NLR of all patients decreased up to 3 months, and then maintained values of around 305 which were also the cut-off points given in the report by Wang et al²³ (Figure 4c). These values were not significantly different at the same time-points of NLR, PNI, and SII.

Discussion

In this study, the 2-year recurrence-free survival rate for resected BCLC-B cases was 48% for those who completed 2 years of treatment and 55.2% for all patients with a history of treatment. These values are better than those previously reported.^{8,24} The inflammation-based prognostic scores of patients with AHCC, namely LNR, PNI, and SII, were maintained at favorable levels after hepatectomy. AHCC-related toxicity and adverse events were not observed in any patient treated with AHCC. In this study, AHCC has been found to be a promising adjuvant therapy for patients with

advanced hepatocellular carcinoma after curative hepatectomy, and this should be verified in randomized trials.

In our study, the 2-year recurrence-free survival rates were 48.0% for complete two-year intake and 55.2% for all intakes. Hence, AHCC showed superior efficacy in preventing recurrence of HCC after curative hepatectomy compared with those reported in the previous reports.^{8,24,25} Although hepatectomy for HCC has the highest local controllability, HCC in BCLC-B HCC is contraindicated for hepatectomy and TACE or systemic therapy are recommended.⁴ By contrast, the superiority of hepatic resection to TACE for patients with BCLC-B HCC was suggested on the basis of the survival analysis of the retrospective study population and propensity-matched pairs.²⁶ Moreover, patients with BCLC-B HCC who underwent hepatectomy were reported to have acceptable prognoses.^{8,24,25} The 2-year recurrence-free survival rates in these 2 reports were about 40% though the specific value of the 2-year recurrence-free survival rate was not given in these articles; hence, it was estimated from the survival curve. The 2-year disease free survival rates of HCC in Eastern and Western Experience Study Groups were presumed to be more than 45% from the disease-free survival curve.²⁵ Therefore, although further studies are needed, the prevention of recurrence of BCLC-B hepatocellular carcinoma by AHCC after hepatic resection seems to be promising.

The analysis of the host-inflammatory response was not performed in the previous study.¹⁹ However, it was recently reported to be associated with cancer progression and patient survival.²⁰ Although the independent prognostic factor for recurrence in this study was hepatic vein invasion positive, and SII, PNI, and NLR scores were not significant factors, the maintenance of these scores at favorable levels during follow-ups might contribute to preventing HCC recurrence. In patients with HCC, severe hepatitis and active inflammation are associated with recurrence after hepatectomy through the NF- κ B pathway-mediated epithelial-mesenchymal transition.²⁷ Recently, the prognostic value of many inflammation-based prognostic scores constructed on systemic inflammatory responses has been reported, in particular, SII.²³ Hence, we evaluated inflammation-based prognostic scores, including SII, PNI, and NLR. No difference was observed in these parameters between patients with and without recurrence within 2 years. However, these parameters were maintained at the favorable levels of prognostic value after hepatectomy, as Wang et al²³ reported that SII, PNI, and NLR were useful indicators of post recurrence survival of HCC patients. These results might be supported by the antioxidant and anti-inflammatory effects of AHCC.^{16-18,28-30} These findings should be validated in a randomized trial setting.

We also evaluated albumin levels and lymphocyte percentages. Albumin levels were recovered after 6 months of hepatectomy, and lymphocyte percentages were maintained

Table 2. Comparison Between Recurrent and No Recurrent Cases.

Variable	Recurrence (+) (n = 13)	Recurrence (-) (n = 12)	P-value
Age (year)			
Mean (SD)	64.8 ± 12.4	69.7 ± 9.2	.2754
Sex			
Male	13	11	.2881
Female	0	1	
Hepatic virus			
HBV	7	3	.3237
HCV	1	1	
NBNC	5	8	
Albumin (g/dL)			
Mean (SD)	4.1 ± 0.4	4.3 ± 0.3	.2626
Total bilirubin (mg/dL)			
Mean (SD)	0.6 ± 0.1	0.7 ± 0.1	.01
ICGR15 (%)			
Mean (SD)	11.5 ± 5.7	9.8 ± 6.0	.4752
NLR			
Mean (SD)	2.8 ± 1.5	3.3 ± 3.2	.5923
SII			
Mean (SD)	539.6 ± 318.3	734.1 ± 840.7	.445
PNI			
Mean (SD)	48.9 ± 6.2	50.8 ± 4.4	.3921
Size (mm)			
Mean (SD)	95.1 ± 35.6	75.4 ± 8.8	.1182
Number			
Solitary	9	11	.1612
Multiple	4	1	
Stage			
II	7	10	.1143
III	6	2	
BCLC stage			
B	13	12	NA
AFP (ng/mL)			
Mean (SD)	59278.3 ± 136068.7	75.4 ± 177.4	.146
PIVKA-II (mAU/mL)			
Mean (SD)	20515.1 ± 40087.3	983.0 ± 1784.1	.1058
AP-factor			
Low	4	9	.027
High	9	3	
Child–Pugh			
A	13	12	NA
Differentiation			
Well	7	7	.5061
Moderate	6	4	
Poor	0	1	
Vascular invasion			
vp+	11	9	.5482
vp-	2	3	
vv+	6	11	.0148
vv-	7	1	

(continued)

Table 2. (continued)

Variable	Recurrence (+) (n = 13)	Recurrence (-) (n = 12)	P-value
Fibrosis ²²			
F0	2	3	.052
F1	2	7	
F2	7	2	
F3	2	0	

HBV, hepatitis B virus surface antigen-positive, hepatitis C virus antibody-negative; HCV, hepatitis B virus surface antigen negative, hepatitis C virus antibody-positive; NBNC, hepatitis B virus surface antigen negative, hepatitis C virus antibody-negative; ICGR15, indocyanine green retention rate at 15 minutes; NLR, neutrophil-to-lymphocyte ratio; SII, systemic immune-inflammation index; PNI, prognostic nutritional index; BCLC stage, Barcelona clinic liver cancer staging classification; AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist II; AP-factor, AFP × PIVKA-II; vp, microscopic tumor thrombus in the portal vein; vv, microscopic tumor thrombus in the hepatic vein; F0, absence of fibrosis; F1, portal fibrosis with no septa; F2, portal fibrosis with infrequent septa; F3, numerous septa but no cirrhosis; SD, standard deviation; NA, not applicable.

Table 3. Logistic Regression Analysis Focused on Recurrence at 2 years After Hepatectomy.

Variable	P-value	Odds ratio	95% CI low	95% CI high
AP-factor				
High	.4755	2.1709	0.2453	19.09
Pre T. Bil				
High	.1151	0.1700	0.0076	1.4964
Hepatic vein invasion				
Positive	.0325	19.25	1.2582	860.72

AFP, alpha-fetoprotein; PIVKA-II, protein induced by vitamin K absence or antagonist II; AP-factor, AFP × PIVKA-II; Pre T. Bil, preoperative total bilirubin; CI, confidence interval.

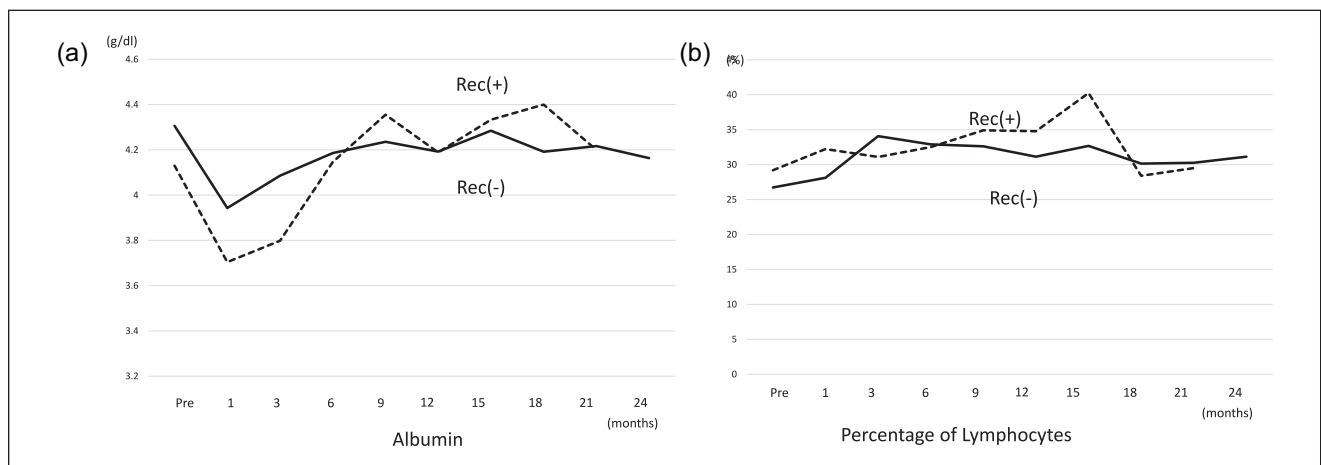


Figure 3. Mean profiles of clinical parameters in all 29 administered cases. (A) Albumin: Serum albumin levels decreased to a minimum in the first postoperative month. Serum levels were lower in the recurrence (+) group at the first postoperative month than in the recurrence (-) group, although the difference was not significant. At postoperative 6 months, the levels in both groups gradually recovered to the preoperative levels. (B) Lymphocyte percentage: Almost no change in lymphocyte percentage in both groups during the follow-up.

at almost the same levels during follow-up. The early recovery of albumin and maintenance of lymphocyte percentages maybe because of AHCC intake because Roman et al³¹ reported that AHCC supplementation improved lymphocyte

percentages. Moreover, AHCC intake could also prolong survival and improve the prognosis of patients with advanced liver cancer, including HCC and cholangiocarcinoma, and delay the gradual decline of their physiological status. No

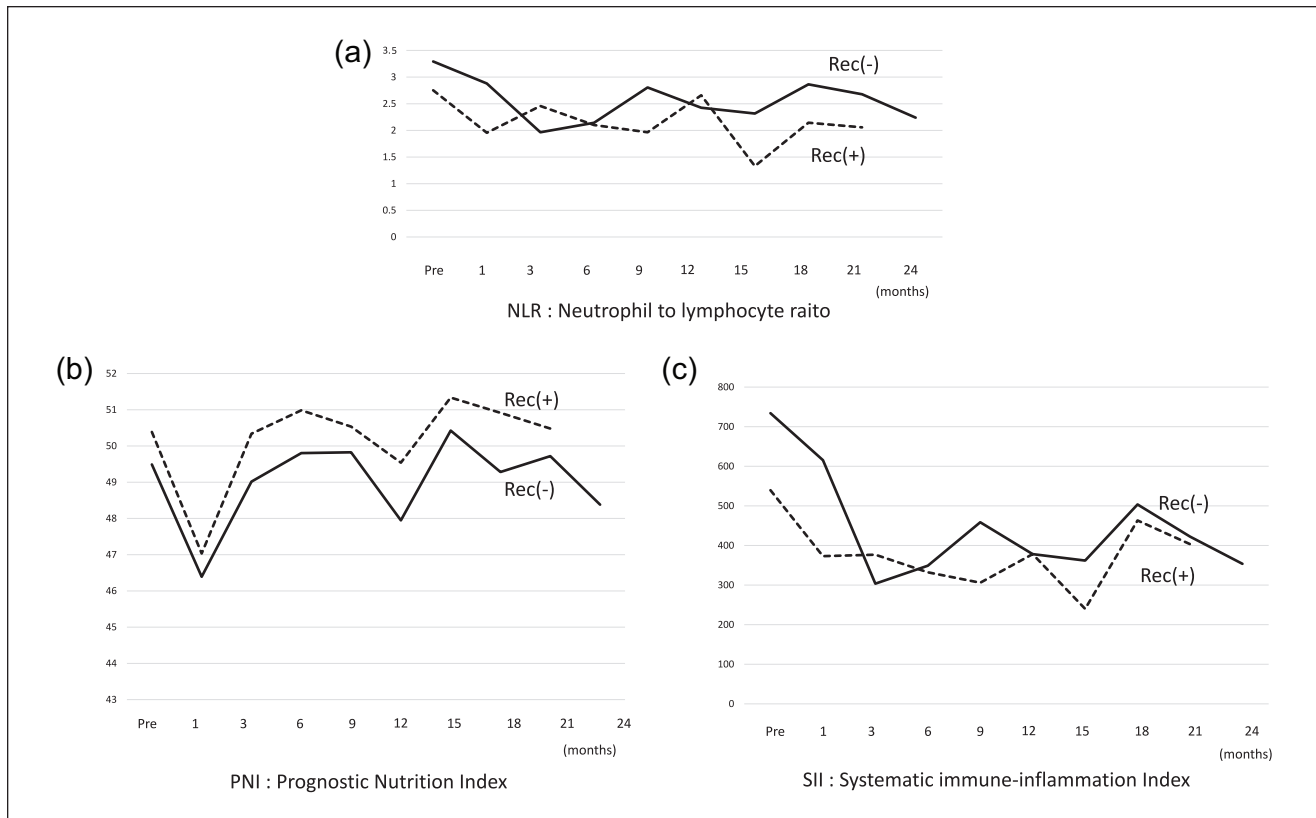


Figure 4. The mean profiles of inflammation-based scores in all 29 administered cases. These values were not significantly different at the same time-points. (A) The change in the neutrophil-to-lymphocyte (NLR) ratio was not different between the groups, and NLR was maintained at <3.5 . (B) Prognostic nutritional index (PNI) score decreased to a minimum in the first postoperative month and gradually recovered. (C) Systemic immune-inflammation index (SII) = $\text{Plt} (\times 10^9/\text{L}) \times \text{NLR}$ decreased up to 3 months and then maintained the same value.

significant difference was observed in albumin levels and lymphocyte percentages, which did not deteriorate after AHCC treatment between the 2 groups with and without AHCC treatment.³² In a previous clinical study of patients with HCC, the prognosis of 113 patients with HCC who underwent curative hepatectomy using AHCC was retrospectively compared to 109 patients who did not receive AHCC.¹⁹ The results indicated that postoperative AHCC intake had a statistically significant effect on several parameters, including improvement of biochemical parameters (cholinesterase activity which is related to protein synthesis by the liver) and hepatitis, prevention of recurrence, and survival rates. The multivariate analysis revealed that AHCC intake was selected as an independent factor for no recurrence or OS.

In our study, recurrence after curative hepatectomy might have been prevented by the immune function of AHCC as described below. AHCC has been reported to exert immune-protective effects against many types of cancer and the effect of AHCC on the components of the immune system, such as NK cells, dendritic cells (DCs), and T cells, including CD4 and CD8 positive T cells.¹⁵ After

AHCC treatment, NK cell activity, which was depressed by an anticancer drug, was reportedly restored and peritoneal macrophage cytotoxicity, nitric oxide production, and cytokine production were stimulated.¹² In patients with breast cancer, who were scheduled to receive postoperative adjuvant anthracycline-based chemotherapy, administration of *L. edodes* mycelia extract maintained patients' quality of life and immune function by inhibiting the increase in the proportion of regulatory T cells to peripheral CD4+ cells.³³ Intake of AHCC increased CD8+ T cell lymphocyte levels after 6 cycles of chemotherapy.³⁴ The antitumor effects of low-dose 5-fluorouracil were potentiated by AHCC in hepatoma 22 tumor-bearing mice through immunomodulation, such as increasing NK cell percentage.¹⁴ AHCC treatment significantly delayed tumor development after B16-F0 melanoma inoculation through an increase in the number of NK cells and tumor antigen-specific CD8+ T cells producing interferon- γ and gammadelta T cells.¹³ AHCC intake in healthy volunteers resulted in an increase in the number of DCs and function of CD11c+DC1s (22).

This study has some limitations. First, this was a single-armed, non-randomized, open, and uncontrolled study.

Second, the number of patients was small. Third, the parameters did not include immune-related markers. In the future, a randomized, controlled study with a large number of patients should be performed for further validation of these results.

Conclusion

Oral intake of AHCC in patients with advanced HCC after curative hepatectomy was safe and maintained lymphocyte percentages and inflammatory markers such as NLR, PNI, and SII at favorable or normal levels accompanying the early recovery of albumin. This study indicated the potential for improved recurrence-free survival compared with that of previously published studies, and these results should be validated in randomized trials.

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Author Contributions

Toshiya Kamiyama: conceptualization, data collection, data analysis, investigation, project administration, visualization, supervision, and writing; Tatsuya Orimo: data collection, data analysis, methodology; Kenji Wakayama: data collection, data analysis, methodology; Tatsuhiko Kakisaka: data collection, data analysis; Shingo Shimada: data collection, data analysis; Akihisa Nagatsu: data collection; Yoh Asahi: data collection; Takeshi Aiyama: data collection; Hirofumi Kamachi: data collection and supervision; Akinobu Taketomi: conceptualization and supervision

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval

All analyses in this study were performed in accordance with the ethical guidelines of Hokkaido University Hospital and according to the Declaration of Helsinki. This study was approved by the Institutional Review Board of Hokkaido University (CRB1180001).

Trial Registration


This clinical trial was registered in the UMIN Clinical Trials Registry. The trial registry: Prevention of recurrence after curative hepatectomy for hepatocellular carcinoma by active hexose correlated compound and URL; <https://upload.umin.ac.jp/>

[cgi-open-bin/ctr/ctr_view.cgi?recptno=R000028079](https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000028079), and ID; UMIN000024396.

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Data Accessibility Statement

The data that support the findings of this study are openly available in the UMIN Clinical Trials Registry.

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