Assessing the characteristics and feasibility of preventing early mortality in patients with hepatocellular carcinoma

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ABSTRACT

Background/Aims: *To determine strategies to prevent early death (ED) and improve the prognosis of patients with advanced hepatocellular carcinoma (HCC).*

Materials and Methods: *Patients who were diagnosed with HCC from January 2012 to June 2017 were considered for the study. Those who survived for ≤6 months from the date of diagnosis were classified into the ED group (n=21) and those who survived for ≥12 months from the date of diagnosis were classified into the non-ED group (n=88).*

Results: *There were significant differences between the ED and non-ED groups in the following conditions: when the patient age was ≥80 years (38.1% vs. 14.8% patients); maximum nodule size was >3 cm (90.5% vs. 27.3%); Child-Pugh class C liver disease was seen (66.7% vs. 26.1%); tumor-node-metastasis (TNM) Stage III-IV tumor was present (85.7% vs. 21.6%); BCLC stage C/D of liver cancer was seen (81.0% vs. 21.6%); JIS score was ≥4 (52.4% vs. 3.4%); serum creatinine level was ≥1.0 mg/dL (52.4% vs. 22.7%); and there was absence of aggressive treatments such as hepatic resection, radiofrequency ablation, transarterial chemoembolization, and chemotherapy (66.7% vs. 4.5%). Logistic regression analysis identified maximum nodule size of >3 cm (p=0.005, OR=58.7, 95% CI=3.43-1003.9), JIS score of ≥4 (p=0.021, OR=12.0, 95% CI=1.44-100.1), and absence of aggressive treatments (p=0.006, OR=24.7, 95% CI=2.47-247.2) as predictive factors for ED. The presence of aggressive treatments significantly improved the 12-month survival rate of advanced HCC patients with BCLC stage C/D (presence vs. absence: 78.3% vs. 7.4%), a maximum nodule size of >3 cm (76.7% vs. 7.7%), and a JIS score of ≥4 (60.0% vs. 0%).*

Conclusion: *Although delayed detection of HCC strongly increased the onset ED, the aggressiveness of HCC treatment is not readily downgraded, and the most aggressive treatment possible should be considered to prevent ED in patients with advanced HCC.*

Keywords: *Barcelona clinic liver cancer (BCLC) staging, hepatocellular carcinoma, mortality, Japanese integrated staging (JIS) score, early death*

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men and the seventh most common cancer in women worldwide. Eastern Asia, including Japan, has a high prevalence of HCC (1). In Japan, the age-standardized incidence rate of liver cancer is 30.7 years per 100,000 people (2). Guidelines for surveillance and early detection of HCC have been well-established, especially in patients with high-risk factors such as chronic hepatitis-B (HBV) or hepatitis-C (HCV) infections (3,4). Antiviral therapies that highly suppress or eradicate hepatitis viruses, such as nucleic acid analogs for chronic HBV infection (5) and interferon-based therapy for chronic HCV infection (6), have shown remarkable progress in decreasing the incidence of HCC.

Further, in addition to traditional treatments such as hepatic resection, liver transplantation, percutaneous ethanol injection therapy, and transarterial chemoembolization (TACE), new treatments for HCC have developed in the last 20 years, such as radiofrequency ablation (RFA) as a locoregional treatment, molecular-targeted therapies, and drug-eluting bead TACE. However, the prognosis of HCC remains poor. HCC was placed as the second leading cause of cancer-related death worldwide and the fifth in Japan, where approximately 30,000 people died of liver cancer in 2012 (7,8).

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This study focused on the early mortality observed after the initial diagnosis of HCC in patients to elucidate the characteristics and risk factors, help prevent early mortality, and determine strategies to improve the overall prognosis of HCC.

MATERIALS AND METHODS

Study design

This retrospective study was conducted at a single center, which is equipped with imaging modalities for HCC detection and offers liver resection, RFA, TACE, molecular-targeted therapies, and palliative care including radiation therapy that is conducted by specialists in HCC.

Patients and definitions

For the classification of early mortality due to HCC, the survival rate of 131 patients who were initially diagnosed with HCC between January 2012 and June 2017 was analyzed using the Kaplan-Meier method (Figure 1). During the observation period, 43 deaths occurred, of which 21 (48.8%) occurred within the first 6 months from the initial HCC diagnosis. Consequently, the survival curve showed a rapid decrease within the first 6 months (to 83.8%) but a relatively slow decrease from 12 to 60 months (from 80.3% to 56.0%) from the date of diagnosis. Based on the survival rate analysis, 109 patients (mean age: 72 [37-99] years; males: 74, females: 35) were classified into either the early death (ED) group, comprising 21 patients who died within 6 months after the initial HCC diagnosis, or the non-early death (non-ED) group, comprising 88 patients who were observed for at least 12 months regardless of whether they survived or died. Eighteen survivors were observed for less than 12 months and 4 patients who died between 6 months and 12 months after the initial HCC diagnosis were excluded because they were considered to have an equivocal status in terms of early versus non-early death.

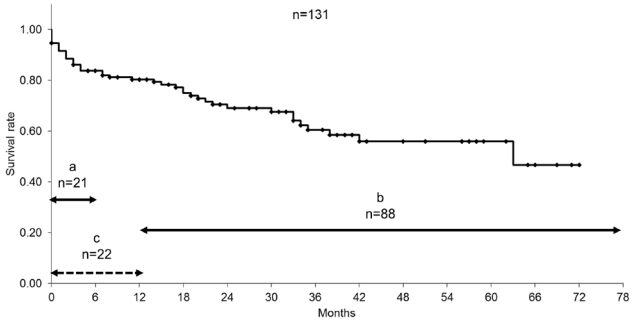

Figure 1. The survival rate of 131 study patients and their classification into the early death and non-early death groups. The survival curve showed a rapid decrease within the first 6 months. According to survival rate, the patients were classified into the early death and non-early death groups as follows:
a) Twenty-one patients who died within 6 months after the initial diagnosis of hepatocellular carcinoma (HCC) were included in the early death group.
b) Eighty-eight patients whose follow-up period was 12 months or more were included in the non-early death group.
c) Eighteen survivors whose observation period was less than 12 months, and 4 patients who died between 6 and 12 months after the initial HCC diagnosis were excluded.

Regarding the quality of HCC treatments, aggressive treatments are defined as those that improve the overall survival of patients with HCC in conjunction with the best supportive care (BSC); these treatments include TACE, hepatic resection, and RFA as curative treatments, and chemotherapy as part of molecular-targeted therapies.

Statistical analysis

Categorical and quantitative variables were analyzed by the χ^2 test and the Mann-Whitney U test, respectively. To elucidate the risk of early mortality due to HCC, logistic regression analysis (forward stepwise selection) was performed. A p-value of <0.05 was considered statistically significant. Survival rates were compared using the generalized Wilcoxon test. The pre-established diagnostic criteria were; the Japanese integrated staging (JIS) score (9), the tumor-node-metastasis (TNM) staging system developed by the Liver Cancer Study Group of Japan (10), the Barcelona Clinic Liver Cancer (BCLC) staging system (11), and the Child-Pugh classification. The best correlation with early death from HCC was determined by Cramer's V, a coefficient of association, using the Cochran-Armitage test. All statistical tests were performed using Ekuseru-Toukei 2015 software (Social Survey Research Information Co., Ltd., Tokyo, Japan).

Ethics statement

To obtain patient consent, the opt-out method (12) was adopted prior to inclusion in the study. This study was approved by the ethics committee at our facility and conformed to the provisions of the Declaration of Helsinki.

RESULTS

The characteristics of the 109 study patients with HCC are shown in Table 1. Most patients were elderly males. In terms of etiology, conventionally chronic HCV infection is the most likely cause of death, but the rate of HCV infection was only 37.6% in this study. Notably, the majority of HCC (57.8%) cases had non-viral causes. Thirty-seven

Table 1. Patient characteristics at the initial diagnosis of HCC (n=109).

Age at diagnosis of HCC	72 (37-99)
Sex (male/female)	74/35
History	
Alcohol drinker	49
Diabetes mellitus	42
Etiology	
HCV/HBV/HCV+HBV	40/6/1
Alcohol	24
Autoimmune liver disease	3
Cryptogenic including NASH	35
Laboratory data	
Albumin (g/dL)	3.8 (1.7-4.8)
Aspartate transaminase (IU/L)	46 (16-483)
Alanine transaminase (IU/L)	33 (9-169)
Lactate dehydrogenase (IU/L)	224 (84-4554)
Alkaline phosphatase (IU/L)	367 (149-3081)
γ-Glutamyltransferase (IU/L)	59 (10-1594)
Total bilirubin (mg/dL)	1.1 (0.4-19.9)
Platelets (×10^4/μL)	12.0 (3.9-222)
Creatinine (mg/dL)	
α-Fetoprotein (ng/mL)	11.5 (2.4-198796.3)
Des-gamma-carboxy prothrombin (mAU/ml)	42 (<10-75000)
Performance status	
0/1/2/3/4	90/7/4/4/4
Hepatic reserve	
Ascites (presence/absence)	18/74
Hepatic coma (presence/absence)	8/84
Portal hypertension (presence/absence)	33 /59
Child-Pugh grade	
A (including non-cirrhosis)/B/C	72/25/12
Tumor characteristics	
Number (1/2/3/4/≥5)	71/10/7/3/18
Maximum diameter (cm)	2.5 (0.5-14.0)
≤3/>3	66/43
Portal vein invasion	15
Intrahepatic vein invasion	4
Lymph node metastasis	2
Extrahepatic metastasis	9
TNM stage (I/II/III/IV)	37/35/16/21
JIS score (0/1/2/3/4/5)	28/33/17/17/9/5
BCLC stage (0/A/B/C/D)	25/42/6/21/15
Initial treatments:	
Aggressive treatments	
Resection	17
Radiofrequency ablation	19
Transarterial (chemo) embolization	51
Molecularly targeted therapy or hepatic arterial infusion chemotherapy	4
Best supportive care	18

HCC: hepatocellular carcinoma; HBV: hepatitis-B virus; HCV: hepatitis-C virus; NASH: non-alcoholic steatohepatitis; JIS: Japanese integrated staging; TNM stage: tumor-node-metastasis staging system developed by the Liver Cancer Study Group of Japan; BCLC stage: Barcelona Clinic Liver Cancer staging system.

(33.9%) patients were classified as having TNM stage III or IV tumors, and 14 (12.8%) patients had a JIS score of 4 or 5. Regarding the BCLC stage, 67 (61.5%) patients were classified as very early or early stage (BCLC-0 or -A), for which curative treatments such as hepatic resection and RFA are recommended, whereas 21 (19.3%) patients and 15 (13.8%) patients were classified as advanced stage (BCLC-C) and terminal stage (BCLC-D) respectively, for which molecular-targeted therapy or BSC is recommended. Of the initial treatments, TACE (46.8%) was administered most frequently, while 18 (16.5%) patients received BSC only.

Comparisons between ED and non-ED groups in terms of the characteristics that affect the prognosis of HCC are shown in Table 2. According to univariate analysis, the ED group consisted of older patients with lower performance status. There was no remarkable difference in the number of nodules (using 3 as the cutoff number), while there were more patients with HCC nodules that were >3 cm in maximum diameter in the ED group than in the non-ED

Table 2. Characteristics of the early death and non-early death groups.

			Univariate analysis	Multivariate analysis		
Variables	Early death group	Non-early death group	p	p	Odds ratio (OR)	95% confidence interval (CI)
Age (<80/≥80 years)	13/8	75/13	0.002	0.107	4.96	0.71-34.72
Sex (male/female)	15/6	59/29	0.458			
Etiology (viral/non-viral)	8/13	39/49	0.396			
PS (0 or 1/2-4)	14/7	83/5	0.002	0.082	6.53	0.79-54.22
Number of nodules (≤3/≥4)	11/10	77/11	0.100			
Maximum nodule size (≤3/>3 cm)	2/19	64/24	<0.001	0.005	58.71	3.43-1003.85
Child-Pugh classification (A/B or C)	7/14	65/23	<0.001			
TNM stage (I or II/III or IV)	3/18	69/19	<0.001			
BCLC stage (0, A, or B/C or D)	4/17	69/19	<0.001			
JIS score (≤3/≥4)	10/11	85/3	<0.001	0.021	12.02	1.44-100.10
Serum creatinine (<1.0/≥1.0 mg/dL)	10/11	68/20	0.009			
Aggressive treatment (presence/absence)	7/14	84/4	<0.001	0.006	24.69	2.47-247.20

PS: performance status; TNM stage: tumor-node-metastasis staging system developed by Liver Cancer Study Group of Japan; BCLC stage: Barcelona Clinic Liver Cancer staging system; JIS: Japanese integrated staging.

group. In the ED group, the Child-Pugh score was worse, and the TNM stage, BCLC stage, and JIS score were higher as compared to the non-ED group. The ED group also had a high serum creatinine level, which can reflect a poor general condition such as poor hemodynamics or hepatorenal syndrome (13). Regarding the initial handling of the disease, aggressive treatments such as hepatic resection, RFA, TACE, and chemotherapy including molecular-targeted therapies were less frequently used in the ED group.

Logistic regression analysis of the above variables showed a significant difference (p<0.01) in the explanatory variables and was performed to determine the predictive factors of early mortality due to HCC. The results indicated that a large maximum nodule diameter (>3 cm), high JIS score (4 or 5), and the absence of initial aggressive treatments were independent predictive factors of early mortality due to HCC. BCLC of stage -C or -D was excluded (Table 2).

The relationship between the initial HCC treatment and BCLC stage in the two groups are shown in Figure 2. The initial treatments performed for 109 patients were not always compatible with the treatments recommended according to their BCLC stage. In the ED group, 15 (71.4%) patients underwent less aggressive treatments than recommended according to BCLC stage, while in the non-ED group, 55 (62.5%) patients underwent similar or more aggressive treatments than recommended (p=0.005). In the ED group, 13 patients were diagnosed as BCLC stages 0, -A, -B, or -C, for which aggressive treatments are typically recommended; however, 7 (53.8%) of these patients received BSC only. Conversely, in the non-ED group, only 4 (4.5%) patients received BSC alone; even though out of the 19 patients with BCLC stages -C or -D, 18 (94.7%) underwent similar or more aggressive treatments than recommended for their BCLC stage. Furthermore, as shown in Figure 3, aggressive treatments improved the prognosis of patients with advanced HCC (BCLC: -C or -D, maximum tumor diameter: >3 cm, or JIS score: 4 or 5). Despite these unfavorable conditions, patients who received more aggressive treatments over and above BSC were able to avoid an early death from HCC.

The correlations between early mortality and pre-established diagnostic criteria are shown in Table 3. The JIS score showed the best correlation with early mortality (Cramer's V=0.646).

Table 3. Relationship between mortality and pre-established diagnostic criteria.

	Early death group	Non-early death group	p	Cramer's V (coefficient of association)
Child-Pugh classification (A/B/C)	7/7/7	68/18/5	<0.001	0.397
BCLC stage (0/A/B/C/D)	0/3/1/9/8	25/39/5/12/7	<0.001	0.513
TNM stage (I/II/III/IV)	1/2/5/13	36/33/11/8	<0.001	0.580
JIS score (0/1/2/3/4/5)	0/2/2/6/7/4	28/31/15/11/2/1	<0.001	0.646

BCLC stage: Barcelona Clinic Liver Cancer staging system; TNM stage: tumor-node-metastasis staging system developed by the Liver Cancer Study Group of Japan; JIS: Japanese integrated staging.

Early death group

Treatment \ BCLC staging	0	A	B	C	D
Hepatic resection	0	1	0	0	0
RFA	0	0	0	0	0
TACE/ TAE	0	1	0	2	1
Chemotherapy	0	0	0	2	0
Best supportive care	0	1	1	5	7

Non-early death group

Treatment \ BCLC staging	0	A	B	C	D
Hepatic resection	3	10	0	3	0
RFA	11	8	0	0	0
TACE/ TAE	10	19	5	6	7
Chemotherapy	0	0	0	2	0
Best supportive care	1	2	0	1	0

Figure 2. Discrepancies between the Barcelona Clinic Liver Cancer (BCLC) stage and the initial treatment recommended according to the BCLC stage in the early death and non-early death groups.
Gray shading indicates the patients who received lower-grade treatments for hepatocellular carcinoma than recommended according to their BCLC stage. Chemotherapy includes molecularly targeted therapy (sorafenib) and hepatic arterial infusion chemotherapy.
BCLC: Barcelona Clinic Liver Cancer; RFA: radiofrequency ablation therapy; TACE: transarterial chemoembolization; TAE: transarterial embolization.

DISCUSSION

The Japanese Association of Clinical Cancer Centers, which has been compiling and analyzing treatment outcomes in 32 hospitals from all over Japan since the 1970s, recently uploaded fresh survival data from the last 10 years about various cancers in Japan on their website (https://kapweb.chiba-cancer-registry.org/full, English is available) for public access. Of the gastrointestinal cancers, the 5-year survival rates for all stages of gastric cancer and colorectal cancer were 68.1% and 70.9%, respectively, and the survival rates at 12 months from the initial diagnosis were 87.1% and 91.7% respectively. Conversely, in cancers associated with poor overall survival rates, such as pancreatic cancer (14), gallbladder cancer (15), and cholangiocarcinoma (16), survival rates showed a sharp decrease within the first 12 months from the initial diagnosis: 44.1% for pancreatic cancer and 60.9% for gallbladder and bile duct cancers. Consequently, the 5-year survival rates are only 8.9% and 24.5%, respectively.

HCC also follows these cancers in terms of poor survival of patients. This study indicated that the majority of HCC mortalities occurred during the first 6 months after diagnosis. Therefore, we suggest that promptly identifying the causes of death within the first 6 months and thereby preventing them could improve the overall prognosis of HCC.

While the prognosis has recently improved for patients with HCC detected during the early stages and treated with curative therapies such as hepatic resection and

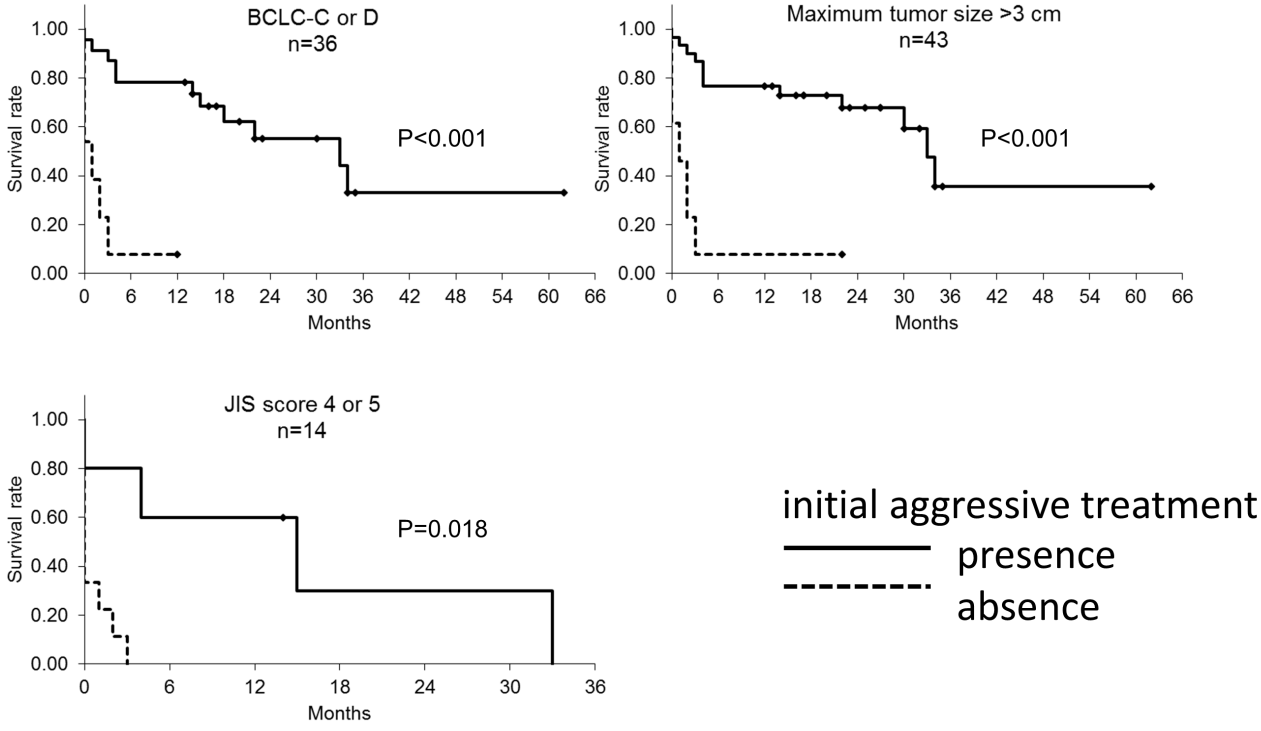

Figure 3. Comparison of survival rate with respect to the presence or absence of initial aggressive treatments in patients with advanced hepatocellular carcinoma (HCC).
Optimal aggressive treatments, beyond best supportive care, prevented early mortality among patients with advanced HCC (defined as BCLC -C or -D, maximum nodule size greater than 3 cm, or JIS score of 4 or 5).

RFA (17), delayed detection has been one of the most important and unresolved causes of the poor prognosis of HCC (18). The major causes of HCC in Japan (80% or more) are chronic HCV/HBV infections. Therefore, 'once in a lifetime' screening for hepatitis-B surface antigen and hepatitis-C antibodies is being promoted in Japan (19). It is recommended that patients with HBV/HCV infection, especially the elderly and those with progression to hepatic fibrosis, undergo regular surveillance for early detection of HCC using tumor markers such as alpha-fetoprotein and des-γ-carboxy prothrombin combined with diagnostic imaging modalities such as ultrasound, contrast-enhanced computed tomography or magnetic resonance imaging (MRI) (3,4,7,20).

However, it is concerning that many patients do not receive testing for HBV/HCV infection (21). In addition, epidemiological reports indicate that the incidence of HCC unrelated to HBV/HCV has been increasing recently in Japan (22,23), and 57.8% of the patients in this study had neither HBV nor HCV infection. Therefore, the traditional algorithm used for early detection of HCC caused by chronic HBV/HCV infection, as a high-risk group of HCC, may not be useful for non-virus-associated HCC cases. The rate of delayed detection of HCC may increase, and consequently, the prognosis of HCC may worsen in the future (24).

Nodules having a size >3 cm or a JIS score of 4 or 5 were important causes of early death from HCC in this study. HCC is often not diagnosed until the advanced or terminal stage, and poor survival of these patients is expected because of the presence of very few effective treatments. However, in this study, patients diagnosed with HCC at an advanced stage were often better off opting for more aggressive treatments such as hepatic resection, TACE, or molecular-targeted therapy rather than facile BSC. There is a wide variety of therapeutic options for early and advanced HCC as compared to other poor-prognosis cancers. Radical hepatic resection and radical RFA are often recommended for patients with early-stage HCC. In this study, TACE was the most frequently administered treat-

ment. For patients with contraindications to TACE, molecular-targeted therapies that have been shown to improve the prognosis of such patients (25) could be considered. The number of molecular-targeted agents approved for advanced HCC is increasing; sorafenib and lenvatinib have recently been approved as first-line molecular-targeted agents in Japan (25). Furthermore, TACE is sometimes re-considered as an alternative option for Child-Pugh C HCC, for which sorafenib is not approved (26).

Curative or tumor-controlling treatments are recommended for patients with BCLC stages of -0, -A, -B, or -C and BSC is recommended for BCLC stage -D. The overall survival rate of BCLC -D patients is predicted to be less than 3 months (11,27). The optimal treatments and predicted overall survival rate corresponding to these five BCLC stages have been adopted worldwide (11, 27). Nevertheless, BCLC of either state -C or stage -D was not an independent predictive factor of early mortality due to HCC in this study. Some believe that aggressive treatments can extend the survival of patients with HCC, even those with BCLC -D (28,29). The results of this study supported this opinion. The ED group included 8 patients with BCLC -D, 7 (87.5%) of whom elected not to receive any other treatment beyond BSC. In contrast, 7 patients in the non-ED group were initially diagnosed with BCLC -D, all of whom were treated with TACE as aggressive treatment.

In Japan, not only the BCLC stage but also a traditional algorithm unique to Japan is adopted to decide treatments for patients with HCC (3,7). Therefore, there may be a discrepancy between the initial treatment selected for HCC and the treatment recommended according to the BCLC stage. Early mortality showed a weaker correlation with the BCLC stage than with the JIS score in this study. Nevertheless, it is noteworthy that in the ED group, the treatment of 5 (55.5%) out of 9 patients with BCLC -C had already been stopped at BSC. An early downgrade to low-grade treatments and early withdrawal from aggressive treatments, especially stopping at BSC, was strongly related to early mortality from HCC. Conversely, aggressive treatments, even for patients with advanced-stage HCC, helped improve the rate of survival. Aggressive treatments prevented early mortality (i.e., within the first 6 months from diagnosis) in patients with not only an advanced BCLC stage but also a maximum tumor diameter of >3 cm or a JIS score of 4 or 5, which were recognized as predictive factors of early mortality.

The number of elderly patients diagnosed with HCC is expected to increase (30). In this study, however, advanced age did not have much effect on early death from HCC. Therefore, early abandonment of treatment for HCC because of advanced age alone may not be appropriate.

Several limitations and biases in our study need to be considered. The sample size was small because this study was conducted in a single hospital. Because few patients visit our hospital from other areas to receive treatment for HCC, the findings of this study are reflective of the conditions in this region only.

Based on these results, we emphasize that although delayed detection of HCC is an ineluctable problem for early mortality from HCC, the most effective treatment (more than BSC) should always be considered, even in patients with advanced HCC, because these efforts may prevent early death from advanced HCC and help improve the overall prognosis of HCC.

A large nodule size, advanced JIS score, and less aggressive initial treatments were predictive of early death from HCC. Screening for early detection of HCC is not practiced sufficiently, especially in patients with unknown risk factors for HCC. For patients with advanced- or terminal-stage HCC, their decision to receive only BSC should be respected. However, it is important that the aggressiveness of HCC treatment is not readily downgraded, and the most aggressive initial treatment possible should be considered even when early detection of HCC is missed. Consequently, prevention of early mortality from HCC, which accounts for a large proportion of the overall mortality from HCC, may improve the prognosis of HCC.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Kitasato University.

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - W.M.; Design - W.M.; Supervision - S.A., K.W.; Materials - W.M., Y.H., T.Y., O.T.; Data Collection and/or Processing - W.M.; Analysis and/or Interpretation - W.M.; Literature Search - S.A., K.W.; Writing Manuscript - W.M.; Critical Review - W.M.

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