Original Article

Body mass index above 24 is beneficial for the 6-month survival rate in hepatocellular carcinoma patients with extrahepatic metastases

Yueh-Shih Chang MD[1], Jen-Seng Huang MD[1], Cho-Li Yen MD[2], Rong-Nan Chien MD[2], Cheng-Hsu Wang MD, PhD[1], Chien-Hong Lai MD[1], Tsung-Han Wu MD[1], Yii-Jeng Lan MD[1], Kun-Yun Yeh MD, PhD[1]

[1]*Division of Hemato-oncology, Department of Internal Medicine, Chang Gung Memorial Hospital, Keelung and Chang Gung University, College of Medicine, Taiwan*
[2]*Liver Research Unit, Division of Hepatogastroenterology, Department of Internal Medicine, Keelung Chang-Gung Memorial Hospital, Taiwan*

Background and Objectives: To investigate the effect of overweight status on the 6-month survival rate in patients with extrahepatic hepatocellular carcinoma (HCC). **Methods and Study Design:** We retrospectively analyzed the records of 51 patients with hepatocellular carcinoma and extrahepatic metastases between 2007 and 2010 before treatment. The associations among overweight status (body mass index [BMI] >24 kg/m^2), demographic variables, and survival outcome were analyzed by univariate and multivariate analysis. **Results:** BMI>24 kg/m^2 was significantly associated with the 6-month survival rate (p=0.042). Gender (p=0.149), Child Pugh classification (p=0.149), Okuda staging (p=0.093), and albumin concentration >3.5 mg/dL (p=0.082) showed marginal survival benefits in univariate analysis. Multivariate analysis confirmed that BMI >24 kg/m^2 was an independent prognostic factor for the 6-month survival rate (p=0.03). **Conclusions:** BMI >24 kg/m^2 was associated with an improved 6-month survival rate in patients with extrahepatic metastatic hepatocellular carcinoma.

Key Words: hepatocellular carcinoma, body mass index, 6-month survival, metastasis, extrahepatic

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of most common cancers leading to death worldwide, and a high incidence rate has been reported in Asian countries including Taiwan.[1,2] Major risk factors such as hepatitis viral infection, alcoholic liver disease, metabolic disorders, and obesity contribute to HCC development according to race, ethnicity, and geographic region.[1,3-5] In particular, obesity has received increased attention because it is seen in nearly 40% of patients with HCC but no chronic hepatitis viral infection in western countries, and several epidemiological studies have found an increased risk of HCC by 17% for overweight persons and by 90% for obese persons compared with individuals at normal weight.[1,6] Overweight and obese status were recognized as poor prognostic factors for HCC within the past decade.

Body mass index (BMI; kg/m^2) is a simple and convenient surrogate measure of body fat distribution in clinical practice and research. The BMI cut-off value was established for the purpose of risk stratification to correlate with disease severity.[7] However, this cut-off BMI value is affected by age, ethnicity, growth patterns, and socioeconomic status.[7] The cut-off BMI values to detect overweight and obese status suggested by Asian population-based studies (22-25 kg/m^2) were lower than those recommended by the World Health Organization (>25 kg/m^2).[7-9] Further, the Working Group on Obesity in China analyzed 239,972 adults and found that a BMI of 24 as a cut-off for overweight status had the best sensitivity and specificity and a BMI of 28 as the cut-off for obesity had a specificity around 90%.[10] Therefore, it is worthwhile to evaluate the association between overweight defined by this lower cut-off BMI value and the prognosis of HCC.

The prognosis of HCC with extrahepatic metastases remains unsatisfactory.[11] Cumulative survival rates at 6, 12, and 24 months after initial diagnosis have been documented to be 44.1%, 21.7%, and 14.2%, respectively.[11] The median survival ranged from 4.9-8.1 months.[11,12] Uchino et al analyzed 342 patients with extrahepatic HCC and found that the 6-month survival rate was an important surrogate measure for treatment outcome if life expectancy and treatment intensity were judged.[12] Further, the

Corresponding Author: Dr Kun-Yun Yeh, Division of Hemato-oncology, Department of Internal Medicine, Chang Gung Memorial Hospital, Keelung & Chang Gung University, College of Medicine, 222 Maijin Road, Keelung, Taiwan.
Tel: 886-2-24329292 ext 2360; Fax: 886-2-2435342
Email: yehtyng@gmail.com
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performance status, Child Pugh score, hepatic reserve, and α-fetoprotein (AFP) concentration were reported to be associated with prognosis,[11,12] but the influence of overweight status on this metastatic illness has yet to be elucidated. The purpose of this study was to assess the effects of overweight status using the cut-off BMI of 24 on relevant demographic parameters and the 6-month survival rate in patients with extrahepatic HCC.

MATERIALS AND METHODS

Patients and diagnosis

A total of 523 patients with HCC were admitted to our institution between January 2007 and December 2010. The diagnosis of HCC was established using ultrasound-guided biopsy or 2 diagnostic modalities identifying the presence of HCC—an imaging study such as contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) in which hyperattenuation in the arterial phase and washout in the late phase were detected along with an elevated AFP level. Extrahepatic metastases were noted in 64 of these patients at the first visit. The diagnosis of extrahepatic metastasis was based upon abdominal ultrasonography, CT, MRI, plain chest radiography, or bone scintigraphy. Tumor biopsies of the metastatic sites were performed when the imaging results were inconclusive. The images, pathology reports, and tumor stages of all 64 patients were reviewed and confirmed by the liver tumor committee of our institution, which included 6 hepatic surgeons, 11 hepatologists, 2 medical oncologists, 1 radiation oncologist, 2 radiologists, and 2 pathologists. Thirteen patients were excluded from the analysis due to inconsistent pathology results, incomplete medical records, previous anti-cancer therapy, or simultaneous occurrence of other neoplasms. A total of 51 consecutive patients were ultimately enrolled in the analysis. All patients were followed up until July 2012, and the median follow-up duration was 7.2 months (range, 1-27 months). This study was approved by the institutional review board of Chang Gung Memorial Hospital.

Data analysis

For each case, we analyzed age, gender, Eastern Cooperative Oncology Group performance status (ECOG PS), history of viral infection including hepatitis B virus (HBV) and hepatitis C virus (HCV), alcohol exposure, comorbid illnesses, hemogram, biochemistry data, serum AFP level, Child Pugh classification and different staging systems (Okuda and Barcelona Clinic Liver Cancer), and BMI before the initiation of treatment. The results of the above continuous variables are expressed as mean ± standard deviation (SD). Survival was defined as the interval from the date of diagnosis of metastatic HCC to the date of death or the last visit before July 2012.

Differences between groups were examined for statistical significance using the Pearson chi-square (χ^2) test or Fisher's exact test for expected numbers per cell <5. The following 15 potential prognostic factors were assessed using binary logistic regression: (1) general condition: gender, age (>65 years or not), Charlson comorbidity index (CCI; >2 or not), performance status (0-2 vs 3-4), the number of metastases (>1 or not), the presence of a lung metastasis, albumin level (>3.5 mg/dL), AFP level (>400 ng/dL), BMI (>24 or not); (2) HBV and HCV status as well as alcohol use; (3) liver function reserve index including Child-Pugh classification (A versus B-C); and (4) staging system including Barcelona Clinic Liver Cancer (BCLC) and Okuda (>2 or not).

All factors that were at least marginally associated with the 6-month survival rate ($p \leq 0.2$) were entered into multivariate analysis. The odds ratio and 95% confidence interval were calculated to evaluate the relative risk. All analyses described above were performed using the Statistical Package for the Social Sciences for Windows version 19.0.

RESULTS

Baseline characteristics are summarized in Table 1. Patients were 14-94 years of age (mean age, 65.1 years), the ratio of men to women was 4:1, and the mean BMI was 21.1 kg/m^2. Chronic infection with HBV or HCV was detected in three-quarters of the patients. The distributions of age, gender, and the positive detection rate of HBV or HCV in this study were in accordance with previously published reports.[12-15] Three-quarters of the patients developed a single metastatic site. The most frequent metastasis location was the lung (60.8%), followed by intra-abdominal seeding (23.5%).

We analyzed each patient's underlying comorbidities because overweight status was related to a higher incidence of comorbidities.[16,17] The comorbidity rate was calculated using CCI, the severity of which was reported as a survival predictor in non-small cell lung cancer, head and neck cancer, and HCC.[18] Nearly 80% of these patients had a CCI >2, indicating that more severe comorbid status occurred in this study. Further, >30% of the patients had a performance status >2, nearly 70% of the patients' Child Pugh classifications were B or C, and the mean albumin level was 2.9 mg/dL. According to BCLC criteria, 54.9% of these patients were in stage C and 45.1% were in stage D. Nearly 80% of the patients belonged to Okuda stage II (47.0%) or stage III (31.4%). Taken together, patients with extrahepatic HCC enrolled in the current investigation were in a relatively poor medical condition. At the time of the analysis, 50 patients had died (98.1%), and the median overall survival time was 7.22 months. The 6-month survival rate was 56.9%.

We stratified patients according to BMI (<24 kg/m^2, N=29; >24 kg/m^2, N=22) to assess the relationships between overweight status and demographic variables in these patients (data not shown). No significant association was noted between BMI and the following variables: gender, age (>65 or not), CCI (>2 or not), performance status (0-2 vs 3-4), number of metastases (>1 or not), occurrence of lung metastasis, presence of HBV/HCV infection, alcohol use, hemoglobin level, white cell count, platelet count, AFP (>400 ng/dL), history of anti-cancer treatment (radiotherapy, chemotherapy, or target therapy) and BCLC staging. Interestingly, the BMI >24kg/m^2 group had more cases with a higher albumin level (>3.5 mg/dL, p=0.044), Child Pugh classification A (p=0.115), and Okuda stage I (p=0.053) and had significantly higher 6-month survival rates (79.1% vs 50.0%, p=0.029). These observations suggested that the status of BMI >24 kg/m^2 reflects a better nutrition status and liver reserve that

Table1. Demographic characteristics of 51 patients with hepatocellular carcinoma and extrahepatic metastases

Variables	Number (%)
Age (years)	65.1±15.8
Gender	
Men	40 (78.4)
Women	11 (21.6)
Body mass index (kg/m^2)	21.1±7.25
HBV, positive	24 (47.1)
HCV, positive	14 (27.5)
Alcohol exposure, positive	14 (27.5)
Number of metastatic site	
1	38 (74.5)
2	11 (21.6)
3	2 (3.9)
Sites of extrahepatic metastases	
Lung	31 (60.8)
Intra-abdominal seeding	12 (23.5)
Bone	6 (11.8)
Adrenal gland	5 (9.8)
Distant lymph nodes	3 (5.8)
Pancreas	3 (5.8)
Brain	2 (3.9)
Bone marrow	1 (1.9)
CCI	
≤2	11 (21.6)
>2	40 (78.4)
ECOG PS score	
≤2	33 (64.7)
>2	18 (35.3)
AFP (ng/L)	15677±45822
White cell count (×10^9/L)	8.1±4.0
Hemoglobin (g/dL)	11.2±2.4
Platelet (×10^3/mm^3)	200±147
Albumin (mg/dL)	2.9±0.8
ALT (mg/dL)	89.9±219
Cr (mg/dL)	1.16±0.6
Child Pugh classification	
A	16 (31.4)
B	21 (41.1)
C	14 (27.5)
BCLC stage	
C	28 (54.9)
D	23 (45.1)
Okuda stage	
I	11 (21.6)
II	26 (47.0)
III	20 (31.4)
Treatment	
Yes	12 (23.5)
No	39 (76.5)
Overall survival (months), median (range)	7.22 (1-27)

CCI: Charlson comorbidity index; ECOG PS: The Eastern Cooperative Oncology Group performance status; AFP: α-fetoprotein; BCLC stage: Barcelona-Clinic Liver Cancer stage.

may be helpful for 6- month survival rate.

Univariate and multivariate analyses were used to evaluate whether the status of BMI >24kg/m^2 was able to independently predict the 6-month survival rate of this advanced illness. As shown in Table 2, BMI >24 kg/m^2 was significantly associated with the 6-month survival rate (p=0.042). Gender (p=0.149), Child Pugh classification (p=0.149), Okuda stage (p=0.093), and albumin level >3.5 mg/dL (p=0.082) showed a marginal survival benefit in univariate analysis. Further, in multivariate analysis with adjustment for gender, albumin >3.5, Child Pugh classification, and Okuda staging, BMI >24 kg/m^2 was an independent prognostic factor for the 6-month survival rate (p=0.03 Table 2).

DISCUSSION

The current study showed that most HCC patients with extrahepatic metastasis at the time of diagnosis in Taiwan had at least one of the following characteristics: advanced stage, unsatisfactory medical performance, one or more severe comorbidities, and poor liver function reserve. Treatment choices are limited, and poor prognosis is predicted. Nonetheless, the survival result of our investigation was in accordance with those reports that enrolled patients with better medical status and liver function reserve,[11,12] suggesting that certain favorable prognostic

Table 2. Univariate and multivariate analysis of prognostic factors for the 6-month survival rate in patients with extrahepatic hepatocellular carcinoma

Prognostic factors	Univariate analysis		Multivariate analysis†	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Gender	2.18 (0.756-6.29)	0.149		
Age >65	1.16 (0.552-2.42)	0.700		
CCI ≥2	0.669 (0.255-1.76)	0.414		
ECOG PS >2	0.755 (0.356-1.60)	0.465		
Number of metastasis (>1)	0.694 (0.307-1.57)	0.231		
Lung metastasis, present	1.22 (0.574-2.58)	0.608		
Albumin ≥3.5	2.36 (0.896-6.23)	0.082		
AFP >400	0.950 (0.458-1.97)	0.890		
HBV, positive	0.773 (0.372-1.60)	0.488		
HCV, positive	1.27 (0.542-2.98)	0.582		
Alcohol use	1.21 (0.516-2.83)	0.662		
Child-Pugh classification, B or C	0.515 (0.209-1.27)	0.149		
BCLC stage, C	1.35 (0.652-2.81)	0.415		
Okuda stage, II or III	0.528 (0.251-1.11)	0.093		
BMI >24	4.27 (1.06-20.3)	0.042	5.20 (1.18-23.0)	0.03

CCI: Charlson comorbidity index; AFP: α-fetoprotein; ECOG PS: The Eastern Cooperative Oncology Group performance status; BCLC stage: Barcelona-Clinic Liver Cancer stage; BMI: body mass index.
†This multivariable analysis is adjusted by gender, albumin, Child-Pugh classification B or C and Okuda stage, II or III.

factors existed among these patients with advanced HCC. Certain demographic variables including age, gender, BMI, performance status, liver function reserve, CCI, serum albumin concentration, AFP level, lung metastasis, hepatitis virus exposure, and tumor stage were associated with survival in patients with HCC.[11,12,14,19-23] After adjustment for these risk factors, BMI >24 kg/m^2 was an independent prognostic factor in the present study. This observation suggested that overweight status using BMI >24 kg/m^2 as the cut-off value at the time of diagnosis affected the survival of patients with extrahepatic HCC.

To our knowledge, few studies have investigated the association between BMI and prognosis in patients with HCC. Ohki et al analyzed 743 naïve HCC patients treated with percutaneous ablation and found that overweight status did not affect HCC recurrence or survival.[24] Mathur et al reported that overweight HCC patients may have better oncologic outcomes following hepatectomy.[25] The current study further showed that overweight status at the time of diagnosis might protect against treatment-naïve patients with extrahepatic HCC and offers survival benefit. However, Utsunomiya et al stratified 328 patients with primary and 68 patients with recurrent HCC according to obese or non-obese status using BMI >25 kg/m^2 as the cut-off value. They found that obesity alone may not affect the surgical outcome of patients with primary HCC, but these patients had poorer 5-year survival rates after undergoing repeat hepatic resection for recurrent HCC.[26] A BMI >30 kg/m^2 was also associated with poor overall survival in patients with HCC who underwent liver transplantation.[27] Taking these reports into consideration, the effect of increased BMI or overweight status on patients with HCC remains controversial, and the apparent discrepancy among studies reflects the differences in study populations, measurement outcomes, and BMI cut-off values.

Relatively high BMI (>24 kg/m^2) showed a favorable survival outcome in the current study, probably because of the association among higher BMI, higher albumin level (3.5 mg/dL), and better liver function reserve (Child Pugh classification A). Although the case number is limited and selection bias is unavoidable in this retrospective analysis, nutritional indicators such as BMI may be important and convenient for physicians to make immediate judgments about such patients with extrahepatic HCC in daily practice.

The use of the 6-month survival rate as a prognosis surrogate is an important measurement for patients with this advanced illness, particularly since most of these patients had unsatisfactory medical conditions. The dilemma between anti-cancer treatment and supportive care remains a tremendous challenge for caring physicians. The findings of the present study suggested that a pre-treatment BMI >24 kg/m^2 is an easy and direct measurement for patients with extrahepatic HCC who may benefit from more aggressive anti-cancer treatment to prolong their survival.

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AUTHOR DISCLOSURES

The authors declare that they have no competing interests and no financial relationship with other organizations sponsoring this research. None of the authors has anything to disclose.

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