Effect of Body Mass Index on Survival after Curative Therapy for non-B non-C Hepatocellular Carcinoma

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ABSTRACT

Background & Aims: The impact of obesity on survival after curative treatment for non-B non-C hepatocellular carcinoma (NBNC-HCC) remains unclear. This study examined the prognostic impact of obesity in patients who received curative therapy for NBNC-HCC.

Methods: A total of 260 patients with NBNC-HCC who underwent curative therapy were analyzed. They included 116 obese patients (44.6%) with a body mass index (BMI) >25 kg/m^2 (obesity group) and 144 control patients (55.4%) with a BMI <25 kg/m^2 (control group). Overall survival (OS) and recurrence-free survival (RFS) rates were compared.

Results: The median observation periods in the obesity and control groups were 3.1 and 3.0 years, respectively. The 1-, 3- and 5-year cumulative OS rates were 93.9%, 77.3% and 56.0% in the obesity group, and 98.8%, 77.3% and 62.1% in the control group, respectively (p = 0.955). The corresponding RFS rates were 74.6%, 28.0% and 19.0% in the obesity group, and 70.0%, 44.3% and 28.9%, in the control group, respectively (p = 0.128). Multivariate analyses identified a serum albumin >4.0 g/dL (hazard ratio [HR], 1.759; 95% confidence interval [CI], 1.007–3.074; p = 0.047) and des-γ-carboxy prothrombin >100 mAU/mL (HR, 0.396; 95% CI, 0.243–0.646; p < 0.001) as independent factors linked to OS. Alkaline phosphatase>300 IU/L (HR, 0.549; 95% CI, 0.367–0.823; p = 0.004) and gamma-glutamyl transferase >100 IU/L (HR, 0.679; 95% CI, 0.471–0.978; p = 0.038) were significant adverse predictors linked to RFS.

Conclusions: Obesity does not affect survival in patients with NBNC-HCC after curative therapy.

Key words: non-B non–C hepatocellular carcinoma – obesity – curative therapy – overall survival – recurrence-free survivall.

INTRODUCTION

Hepatocellular carcinoma (HCC) is diagnosed in more than half a million people worldwide each year, and therefore it is a major health problem worldwide. Hepatocellular carcinoma is the fifth most common cancer in the world and the third most common cause of cancer-related death [1–3]. Although most cases of HCC are attributable to chronic liver disease resulting from chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections, a substantial proportion of HCC patients are negative for markers of HBV surface antigen (HBsAg) and HCV antibody (HCVAb) (non-B non-C HCC [NBNC-HCC]). The frequency of NBNC-HCC has been reported to range from 5 to 15% [4–9], and the number of NBNC-HCC patients in Japan has recently been increasing [5, 6, 8-10].

Hepatocellular carcinoma often recurs. The prognosis of HCC is generally poor because of a high post-treatment recurrence rate characterizing HCC. Recurrence only occurs at intrahepatic sites in 68–96% of patients [11-13]. Therefore, the identification of prognostic factors and optimal management for HCC recurrence are essential for improving survival, even after curative treatment.

Obesity is a major health problem throughout the world because it is perceived as an alarming threat directly related to lifestyle [14]. The World Health Organization (WHO) estimates that, currently, more than 1.5 billion adults worldwide are overweight, of which at least 500 million are obese. Obesity is linked to several health disorders, such as hypertension, cardiovascular disease, and diabetes mellitus (DM), which are collectively known as "metabolic syndrome" [15]. Obesity is also now widely accepted as a significant risk

factor for the development of various types of cancer [16, 17]. Two large population prevalence studies have reported that HCC is also associated with obesity [14, 18]. Hepatocellular carcinoma eventually develops more often in obese patients with cryptogenic liver cirrhosis (LC) than in those with HCV or HBV. This indicates that obesity-related cryptogenic LC carries a risk of evolving to HCC that rivals the risk of this clinical outcome in patients with HCV or HBV-related LC. However, it remains unknown whether obesity constitutes an additional risk in terms of poorer survival after curative therapy for NBNC-HCC. Therefore, the present study aimed to investigate the relationship between obesity and survival in NBNC-HCC patients who underwent curative treatment.

PATIENTS AND METHODS

Patients

A total of 1,636 treatment-naïve HCC patients received curative therapy at our institution between June 2001 and July 2012. Curative therapy was defined as therapy resulting in no apparent viable tumor on dynamic computed tomography (CT) performed within 1 month after initial treatment. Of these, 283 HCC patients (17.3%) had NBNC-HCC, negative for both HBsAg and HCVAb. HBsAg and HCVAb were assessed using commercial enzyme immunoassay kits (Dainabot, Tokyo, Japan). Patients with excessive alcohol intake (n = 21) and patients with primary biliary cirrhosis (n = 2) were excluded from the study. Excessive alcohol consumption was defined as an alcohol intake >80 g/day [19]. A total of 260 NBNC-HCC patients were analyzed in the present study (Fig. 1). After diagnosis of HCC, the most appropriate therapeutic procedure was selected by discussions with surgeons and physicians, according to the tumor characteristics and underlying liver functional reserve of each patient. Patients were classified into two groups: the obesity group with a body mass index (BMI) of > 25 kg/m^2 (n = 116, 44.6%) (range, 25.0-38.9 kg/m^2; median value, 27.3 kg/m^2) and the control group with a BMI of <25 kg/m^2 (n = 144, 55.4%) (range, 14.1-24.9 kg/m^2; median value, 21.9 kg/m^2). WHO defines obesity as a BMI of >30 kg/m^2 [20]. However, in Japan, the proportion of the population with a BMI of >30kg/m^2 has been reported to be no more than 2-3%, in contrast to the 20-30% prevalence in Western countries. In Japan, the definition of obesity is proposed to be a BMI of >25 kg/m^2 because of the increase in incidence of obesity-related disorders in the population with a BMI of >25 kg/m^2 [21, 22]. Overall survival (OS) and recurrence-free survival (RFS) rates were compared between the two groups. A diagnosis of diabetes mellitus (DM) was based on past medical history or 75-g oral glucose tolerance test results [23].

Written informed consent was obtained from all patients prior to each therapy, and the study protocol complied with all of the provisions of the Declaration of Helsinki. This study was approved by the Ethics Committee of the Osaka Red Cross Hospital, Japan. The need for written informed consent in the current study was waived, because the data were analyzed retrospectively and anonymously. The present study comprised a retrospective analysis of patient records registered in our database, and all treatments were conducted in an open-label manner.

HCC diagnosis

Hepatocellular carcinoma was diagnosed using abdominal ultrasound and dynamic computed tomography (CT) scans (hyperattenuation during the arterial phase in all or some parts of the tumor and hypoattenuation in the portal-venous phase) and/or magnetic resonance imaging (MRI), based mainly on the recommendations of the American Association for the Study of Liver Diseases [24]. Arterial- and portal-phase dynamic CT images were obtained at approximately 30 s and 120 s, respectively, after the injection of contrast material. Hepatocellular carcinoma stage was determined using the Liver Cancer Study Group of Japan staging system [25]. This staging system assumes three conditions: (1) a maximum tumor diameter of <2 cm; (2) a single tumor present; and (3) no vascular invasion of the tumor. The staging system is as follows: if all three conditions are met, the tumor is classified as stage I; if two conditions are met, it is classified as stage II; if only one condition is met, it is classified as stage III; and

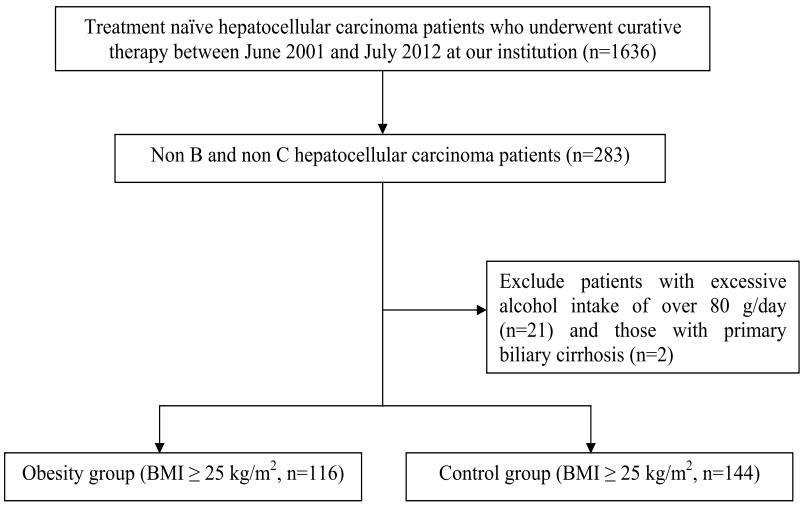

Fig. 1. Study profile.

if none of the conditions are met, it is classified as stage IV. Hepatocellular carcinoma was confirmed pathologically only in patients who underwent surgery.

Comorbid diseases

The presence of diseases that could have a potential impact on the prognosis was recorded, including hypertension, cardiovascular diseases, respiratory diseases, cerebrovascular diseases, and DM. Recently, the presence of DM has been reported to be a worse prognostic factor in HCC patients [26, 27].

Follow-up

Follow-up after each therapy consisted of periodic blood tests and monitoring of tumor markers, including α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP), using chemiluminescent enzyme immunoassays (Lumipulse PIVKAII Eisai, Eisai, Tokyo, Japan). Dynamic CT scans and/or MRI were obtained every 2–4 months after each therapy. Chest CT, whole abdominal CT, brain MRI, and bone scintigraphy were performed when extrahepatic HCC recurrence was suspected.

Statistical analysis

Data were analyzed using univariate and multivariate analyses. Continuous variables were compared using unpaired t-tests and categorical variables were compared using Fisher's exact tests. Time to recurrence was defined as the interval between each therapy and first confirmed recurrence. For analysis of RFS, follow-up ended at the time of first recurrence; other patients were censored at their last follow-up visit or the time of death from any cause without recurrence. For analysis of OS, follow-up ended at the time of death from any cause, and the remaining patients were censored at the last follow-up visit. The cumulative OS and RFS rates were calculated using the Kaplan-Meier method, and tested using the log-rank test. Factors with a p value <0.05 in univariate analysis were subjected to multivariate analysis using the Cox proportional hazards model. These statistical methods were used to estimate the interval from initial treatment. Data were analyzed using SPSS software, version 11.0 (SPSS Inc., Chicago, IL, USA) for Microsoft Windows. Data are expressed as means ± standard deviation (SD). Values of p <0.05 were considered to be statistically significant.

RESULTS

Baseline characteristics

The baseline characteristics of the patients in the two groups are shown in Table I. The median observation periods were 3.1 years (range, 0.3–11.4 years) in the obesity group and 3.0 years (range, 0.3–10.0 years) in the control group.

In the obesity group, surgical resection was performed in 47 patients (40.5%); percutaneous ablation therapy, such as radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI) were performed in 59 patients (50.9%); and transcatheter arterial chemoembolization (TACE) was performed in 10 patients (8.6%). In the control group, surgical resection was performed in 70 patients (48.6%), RFA or PEI in 65 patients (45.1%), and TACE in 9 patients (6.3%) (p = 0.383). In terms of total bilirubin (p = 0.001), prothrombin time (PT) (p = 0.016), and platelet count (p = 0.016), significant differences were observed in the two groups, indicating that the obesity group had more advanced background liver disease than the control group, although in terms of Child-Pugh classification, the difference did not reach significance (p = 0.518). In comorbid diseases, the proportion of hypertension in the obesity group was significantly higher than that in the control group (p = 0.001).

Cumulative OS and RFS rates in the two groups

The 1-, 3- and 5-year cumulative OS rates were 93.9%, 77.3%, and 56.0% in the obesity group, and 98.8%, 77.3%, and 62.1% in the control group, respectively (p = 0.955, Fig. 2). The corresponding RFS rates were 74.6%, 28.0%, and 19.0% in the obesity group, and 70.0%, 44.3%, and 28.9% in the control group, respectively (p = 0.128, Fig. 3).

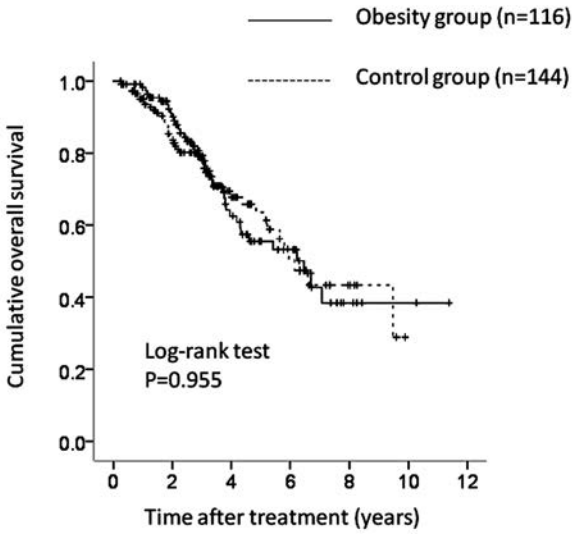

Fig. 2. The cumulative overall survival (OS) rates between the obesity group and the control group.

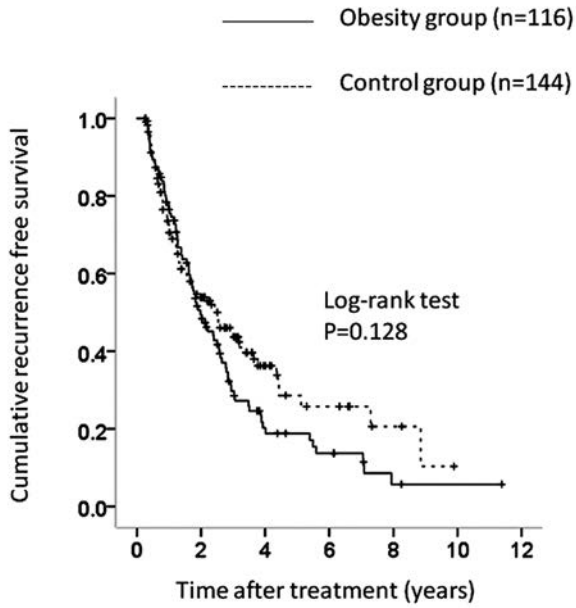

Fig. 3. The cumulative recurrence-free survival (RFS) rates between the obesity group and the control group.

Table I. Baseline characteristics of the obesity group and the control group.

Variables	Obesity group (n=116)	Control group (n=144)	P-value
Age (years)	68.7 ± 8.7	69.1 ± 9.9	0.731[a]
Gender, male/female	84 / 32	115 / 29	0.186[b]
HCC stage			
Stage I / II / III / IV	19 / 62 / 32 / 3	21 / 76 / 38 / 9	0.570[b]
Initial treatment for HCC			
Surgery / Ablation / TACE	47 / 59 / 10	70 / 65 / 9	0.383[b]
Maximum tumor size (cm)	3.6 ± 2.5	4.2 ± 2.9	0.102[a]
Tumor number, single / multiple	73 / 43	96 / 48	0.601[b]
Child-Pugh classification			
Child-Pugh A / B	96 / 20	127 / 17	0.518[b]
AST (IU/L)	44.3 ± 19.6	43.4 ± 25.7	0.761[a]
ALT (IU/L)	35.5 ± 21.1	33.2 ± 34.6	0.522[a]
LDH (IU/L)	234.5 ± 52.2	238.9 ± 154.3	0.769[a]
ALP (IU/L)	375.1 ± 174.7	361.9 ± 169.0	0.537a
GGT (IU/L)	157.5 ± 182.7	165.9 ± 216.4	0.737[a]
Serum albumin (g/dL)	3.85 ± 0.51	3.92 ± 0.52	0.241[a]
Total bilirubin (mg/dL)	1.08 ± 0.64	0.85 ± 0.49	0.001[a]
Prothrombin index (%)	83.7 ± 19.5	89.1 ± 17.0	0.016[a]
Platelets ($\times 10^4/mm^3$)	13.0 ± 7.0	15.1 ± 7.2	0.016[a]
White blood cell count ($\times 10^4/mm^3$)	0.53 ± 0.17	0.57 ± 0.19	0.153[a]
AFP (ng/mL)	120.7 ± 368.2	1398.4 ± 10831.5	0.205[a]
DCP (mAU/mL)	2864.4 ± 11080.5	6129.6 ± 42746.7	0.430[a]
Comorbid diseases			
Hypertension, yes/no	84 / 32	76 / 68	0.001[b]
Cardiovascular disease, yes/no	26 / 90	35 / 109	0.770[b]
Respiratory disease, yes/no	15 / 101	25 / 119	0.388[b]
Cerebrovascular disease, yes/no	16 / 100	20 / 124	>0.999[b]
Diabetes mellitus, yes/no	62 / 54	66 / 78	0.262[b]

Data are expressed as number or mean ± standard deviation. HCC; hepatocellular carcinoma, TACE; transcatheter arterial chemoembolization, AST; aspartate aminotransferase, ALT; alanine aminotransferase, LDH; lactate dehydrogenase, ALP; alkaline phosphatase, GGT; gamma glutamyl transpeptidase, AFP; alpha-fetoprotein, DCP; des-γ-carboxy prothrombin, [a]; unpaired t test, [b]; Fisher's exact test

Univariate and multivariate analysis of factors contributing to OS

Univariate analysis identified the following factors as being significantly associated with OS for all cases (n = 260): Child-Pugh classification; HCC stage; tumor number; total bilirubin >1 mg/dL; serum albumin >4.0 g/dL; aspartate aminotransferase (AST) >40 IU/L; alkaline phosphatase(ALP) >300 IU/L; gamma-glutamyl transpeptidase(GGT) >100 IU/L; PT >80% and DCP >100 mAU/mL (Table II). The hazard ratios (HRs) and 95% confidence intervals (CIs) calculated using multivariate analysis for the 10 factors that were revealed to be significant in univariate analysis are shown in Table II. Serum albumin >4.0 g/dL and DCP >100 mAU/mL were found to be significant predictors linked to OS in multivariate analysis.

Univariate and multivariate analysis of factors contributing to RFS

Univariate analysis identified the following factors as significantly associated with RFS for all cases (n = 260): Child-Pugh class; HCC stage; tumor number; serum albumin >4.0 g/dL; AST >40 IU/L; ALP >300 IU/L; GGT >100 IU/L; platelets $>13\times10^4/mm^3$; PT >80%, and AFP >10 ng/mL (Table III). The HRs and 95% CIs calculated using multivariate analysis for the 10 factors, which were found to be significant in univariate analysis, are shown in Table III. ALP >300 IU/L and GGT >100 IU/L were significant adverse prognostic factors linked to RFS.

Causes of death

Thirty-nine patients in the obesity group (33.6%) died during the follow-up period. The causes of death were HCC recurrence in 22 patients, liver failure in 13 patients, and miscellaneous causes in four patients. Forty-five patients in the control group (31.3%) died during the follow-up period, and the causes of death were HCC recurrence in 25 patients, liver failure in 13 patients, and miscellaneous in 7 patients.

HCC recurrence

In the present study, 84 patients in the obesity group (72.4%) and 83 in the control group (57.6%) had HCC recurrences during

Table II. Univariate and multivariate analysis of factors contributing to overall survival for all cases (n=260).

		Univariate analysis	Multivariate analysis		
Variables	Number of patients	P-value[a]	HR	95% CI	P-value[b]
Age >70 (yes / no)	137 / 123	0.867			
Gender (male / female)	199 / 61	0.739			
Child-Pugh classification (A / B)	223 / 37	0.015	0.974	0.507-1.871	0.938
HCC stage (I, II / III, IV)	178 / 82	0.001	0.778	0.372-1.627	0.505
Maximum tumor size >3cm (yes / no)	136 / 124	0.078			
Tumor number (single / multiple)	169 / 91	0.001	0.744	0.357-1.553	0.431
Total bilirubin > 1.0mg/dL (yes / no)	88 / 172	0.020	0.791	0.460-1.359	0.396
Serum albumin > 4.0g/dL (yes / no)	131 / 129	<0.001	1.759	1.007-3.074	0.047
AST > 40IU/L (yes / no)	129 / 131	0.039	0.743	0.450-1.225	0.244
ALT > 30IU/L (yes / no)	120 / 140	0.484			
ALP > 300IU/L (yes / no)	148 / 112	0.001	0.773	0.449-1.333	0.355
GGT > 100IU/L (yes / no)	132 / 128	0.040	0.854	0.511-1.426	0.546
White blood cell > 0.5×104/mm3 (yes / no)	152 / 108	0.900			
LDH > 220 IU/L (yes / no)	125 / 135	0.118			
Platelets >13×10^4/mm^3 (yes / no)	134 / 126	0.314			
Prothrombin time >80% (yes / no)	176 / 84	0.014	1.214	0.674-2.185	0.518
AFP >10ng/mL (yes / no)	115 / 145	0.148			
DCP >100mAU/mL (yes / no)	143 / 117	0.001	0.396	0.243-0.646	<0.001
Diabetes mellitus (yes / no)	128 / 132	0.282			
Body mass index >25kg/m^2 (yes / no)	116 / 144	0.955			

OS; overall survival, HR; hazard ratio, 95% CI; 95% confidence interval, HCC; hepatocellular carcinoma, AST; aspartate aminotransferase, ALT; alanine aminotransferase, ALP; alkaline phosphatase, GGT; gamma glutamyl transpeptidase, LDH; lactate dehydrogenase, AFP; alpha-fetoprotein, DCP; des-γ-carboxy prothrombin, [a]; Log-rank test, [b]; Cox proportional hazard model

the follow-up period. The patterns of HCC recurrence after initial treatment for HCC in the obesity group were as follows: single HCC recurrence in the liver in 33 patients; multiple HCC recurrences in the liver in 46 patients; multiple HCC recurrences in the liver with lymph node metastases in 3 patients; multiple HCC recurrences in the liver with peritoneal dissemination in 1 patient and portal vein tumor invasion in 1 patient. The patterns of HCC recurrence after initial treatment for HCC in the control group were as follows: single HCC recurrence in the liver in 33 patients; multiple HCC recurrences in the liver in 38 patients; multiple HCC recurrences in the liver with lymph node metastases in 2 patients; multiple HCC recurrences in the liver with lung metastases in 7 patients; multiple HCC recurrences in the liver with peritoneal dissemination in 2 patients and bile duct invasion in 1 patient.

Treatment methods for the first HCC recurrence in the obesity group included surgical resection in 5 patients, percutaneous ablation therapy in 38 patients, TACE in 23 patients, systemic chemotherapy in 1 patient, and no specific treatment in 17 patients. Treatment methods for the first recurrence in the control group included surgical resection in 4 patients, percutaneous ablation therapy in 39 patients, TACE in 21 patients, systemic chemotherapy in 6 patients, and no specific treatment in 13 patients.

Subgroup analyses according to Child-Pugh classification

In terms of total bilirubin, serum albumin and platelet count, which are considered to reflect hepatic functional reserve, significant differences in the two groups were observed in baseline characteristics. Therefore, we performed subgroup analyses according to Child-Pugh classification. In patients with Child-Pugh A (n = 223), there were 96 patients in the obesity group and 127 patients in the control group. No significant difference in OS was observed between the two groups (p = 0.616, Fig. 4A). However, with regard to RFS, the obesity group had a significantly worse prognosis than the control group (p = 0.018, Fig. 4B). In patients with Child-Pugh B (n = 37), there were 20 patients in the obesity group and 17 patients in the control group. No significant difference was observed in OS between the two groups (p = 0.160, Fig. 5A). However, with regard to RFS, interestingly,

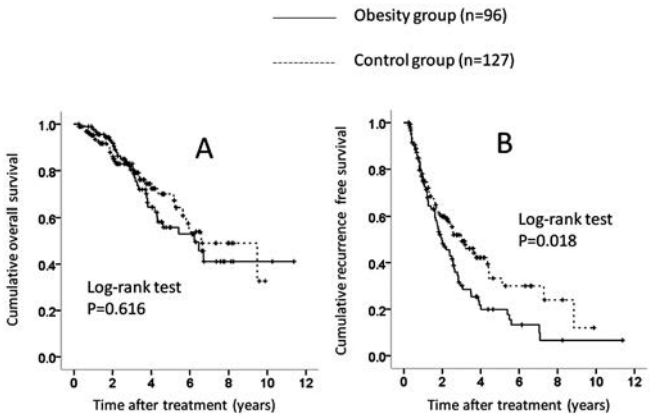

Fig. 4. Subgroup analyses in patients with Child-Pugh A.

Table III. Univariate and multivariate analysis of factors contributing to recurrence free survival for all cases (n=260).

		Univarate analysis	Multivariate analysis		
Variables	Number of patients	P-value[a]	HR	95% CI	P-value[b]
Age >70 (yes / no)	137 / 123	0.457			
Gender (male / female)	199 / 61	0.845			
Child-Pugh classification (A / B)	223 / 37	0.001	0.775	0.473-1.270	0.313
HCC stage (I, II / III, IV)	178 / 82	<0.001	0.818	0.463-1.446	0.490
Maximum tumor size >3 cm (yes / no)	136 / 124	0.484			
Tumor number (single / multiple)	169 / 91	<0.001	0.645	0.370-1.124	0.122
Total bilirubin >1.0 mg/dL (yes / no)	88 / 172	0.189			
Serum albumin >4.0 g/dL (yes / no)	131 / 129	0.004	0.984	0.661-1.464	0.937
AST >40IU/L (yes / no)	129 / 131	0.006	0.982	0.696-1.387	0.919
ALT >30IU/L (yes / no)	120 / 140	0.275			
ALP >300 IU/L (yes / no)	148 / 112	<0.001	0.549	0.367-0.823	0.004
GGT >100 IU/L (yes / no)	132 / 128	<0.001	0.679	0.471-0.978	0.038
White blood cell >0.5×10^4/mm^3 (yes / no)	152 / 108	0.790			
LDH >220 IU/L (yes / no)	125 / 135	0.272			
Platelets >13×10^4/mm^3 (yes / no)	134 / 126	0.036	0.910	0.642-1.289	0.594
Prothrombin time >80% (yes / no)	176 / 84	<0.001	1.372	0.890-2.115	0.152
AFP >10ng/mL (yes / no)	115 / 145	0.045	0.964	0.689-1.348	0.829
DCP >100mAU/mL (yes / no)	143 / 117	0.064			
Diabetes mellitus (yes / no)	128 / 132	0.751			
Body mass index >25kg/m^2 (yes / no)	116 / 144	0.128			

RFS; recurrence free survival, HR; hazard ratio, 95% CI; 95% confidence interval, HCC; hepatocellular carcinoma, AST; aspartate aminotransferase, ALT; alanine aminotransferase, ALP; alkaline phosphatase, GGT; gamma glutamyl transpeptidase, alanine aminotransferase, LDH; lactate dehydrogenase, AFP; alpha-fetoprotein, DCP; des-γ-carboxy prothrombin, [a]; Log-rank test, [b]; Cox proportional hazard model

the obesity group had a significantly better prognosis than the control group in contrast to patients with Child-Pugh A (p = 0.001, Fig. 5B).

Subgroup analyses in patients with or without DM

Patients with DM were 62 patients in the obesity group and 66 in the control group. In patients with DM, there were no significant differences in OS (p = 0.501, Fig. 6A) and RFS (p = 0.539, Fig. 6B) among the two groups. Patients without DM included 54 patients in the obesity group and 78 in the control group. In patients without DM, there was no significant difference in OS among the two groups (p = 0.656) (Fig. 7). The rate of RFS in the obesity group without DM tended to be lower than that in the control group without DM, but this difference did not reach significance (p = 0.078).

Further analysis according to BMI

According to the WHO classification, we classified the obese patients into two groups (patients with a BMI of >30

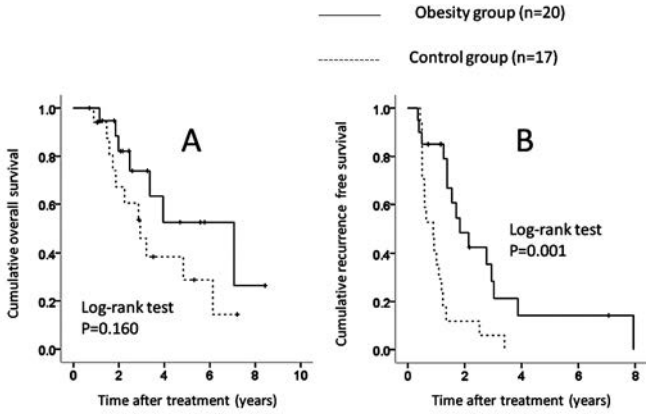

Fig. 5. Subgroup analyses in patients with Child-Pugh B.

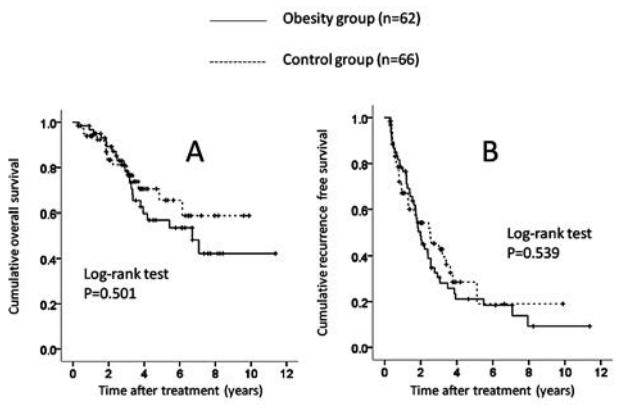

Fig. 6. Subgroup analyses in patients with diabetes mellitus.

kg/m^2 [n = 24] and those with a BMI of <30 kg/m^2 [n = 92]. [15]. Similarly, we classified the control patients into two groups (patients with a BMI of >18.5 kg/m^2 [n = 125] and those with a BMI of <18.5 kg/m^2 [n = 19]). We compared OS and RFS rates in these four groups. In terms of OS, there was no significant difference in these four groups (overall significance; p = 0.267) (Fig. 8A). In terms of RFS, the difference in the four groups did not also reach significance (overall significance; p = 0.105) (Fig. 8B).

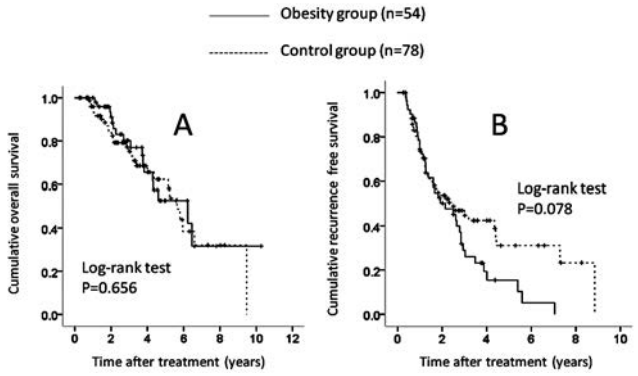

Fig. 7. Subgroup analyses in patients without diabetes mellitus.

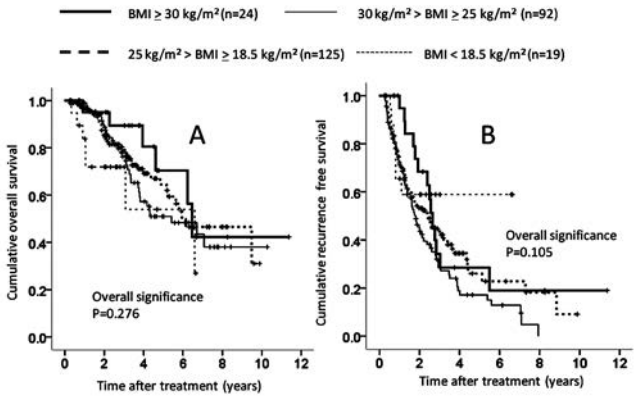

Fig. 8. Kaplan-Meier curves using classification into four groups according to BMI.

DISCUSSION

To the best of our knowledge, this is the first reported comparative study to investigate the relationship between obesity and survival in NBNC-HCC patients who have undergone curative therapy. Although several investigators have reported that obesity is associated with liver carcinogenesis [14, 16, 17, 18, 28, 29], whether obesity is a prognostic factor in NBNC-HCC patients who undergo curative therapy remains unclear. Therefore, the current study was performed to determine this issue.

In our study, differences in OS and RFS between the obesity and control groups did not reach significance. In addition, in our further analysis using classification into four groups according to BMI, the difference between these four groups did not reach significance in terms of both OS and RFS. These results indicate that obesity did not affect survival after curative therapy for NBNC-HCC patients. One possible reason for these results is that in Japan, the proportion of extremely obese patients with a BMI >35 kg/m^2 who have a higher potential risk of HCC development is reduced. Indeed, in the current study, there were only five patients (1.9%) with a BMI >35 kg/m^2. The distribution of BMI appears to be quite different between Japan and the Western countries, which have a large number of extremely obese patients [14, 30].

With regard to baseline characteristics, total bilirubin, prothrombin, and platelet count, which reflect the degree of liver fibrosis in the obese group, were significantly worse than those in the control group. However, for Child-Pugh classification, the difference between the two groups did not reach significance. Obesity induces steatosis and increases oxidative stress, as well as chronic inflammation in the liver, and therefore it places people at risk of developing cirrhosis [31]. These facts may have been associated with more advanced liver fibrosis in our obesity group patients. In addition, 128 (49.2%) out of 260 patients had DM in the current study. A population-based study from the United States demonstrated that, in HCC patients with unknown causes, 47% had DM, and DM was found to be an independent risk factor for liver carcinogenesis, regardless of any etiologies of background liver disease [32]. Our results are consistent with this previous report [32].

In our analysis according to Child-Pugh classification, in patients with Child-Pugh A, the obesity group had a significantly worse prognosis than the control group in terms of RFS, whereas in patients with Child-Pugh B, the obesity group had a significantly better prognosis than the control group in terms of RFS. Obesity, which reflects good nutritional and immunological status, may be associated with favorable clinical outcomes in NBNC-HCC patients with more advanced background disease after curative therapy. In our subgroup analyses in patients with or without DM, no significant differences were observed, although in patients without DM, the obesity group patients tended to have a worse prognosis compared with the control group patients in terms of RFS. Metabolic disorders may not be associated with clinical outcomes after curative therapy for NBNC-HCC patients.

In our multivariate analysis, serum albumin >4.0 g/dL was found to be a favorable predictive factor linked to OS. We have previously reported that a low serum albumin level was associated with poor clinical outcomes in patients with HCV-related HCC who underwent RFA [33]. In HCV-related HCC patients with a low serum albumin level, as well as NBNC-HCC patients with a low serum albumin level, branched chain amino acid therapy may be recommended [33]. In our study, multivariate analysis identified high DCP levels as the strongest adverse prognostic factor linked to OS, although in terms of RFS, it was not shown to be a significant factor in multivariate analysis. High DCP levels indicate biologically aggressive HCC tumors [34]. Kaibori et al reported that preoperative serum DCP levels are a prognostic indicator in NBNC-HCC [4]. Our results are in agreement with these previous reports, suggesting that NBNC-HCC patients with high pretreatment DCP levels require close observation, even after curative therapy, to optimize their clinical outcomes.

Notably, an ALP value of >300 IU/L and GGT value of >100 IU/L were found to be significant adverse predictive factors linked to RFS in our multivariate analysis. Yu et al demonstrated that preoperative ALP levels could be used to monitor and predict recurrence in HCC patients. Several studies reported that a high level of GGT is related to a higher incidence of HCC development and recurrence [35-37]. Ju et al reported that a high GGT level is associated with tumor characteristics, such as tumor size and a lower serum albumin level [38]. In NBNC-HCC patients with a high level of ALP or GGT prior to therapy, careful follow-up examination after therapy is required.

There are several limitations to the present study. First, it was a single-center retrospective study. Second, in our study, the difference of median value between the obesity group and the control group and the number of patients with a BMI of >30 kg/m^2 or with a BMI of <18.5 kg/m^2, which could influence on survival were fairly small. In addition, there seems to be a complex relationship between overweight and survival [14, 21, 22, 30]. Hence, our study results should be interpreted with caution and other prognostic factors than BMI should also be fully taken into account when evaluating the prognosis in patients with NBNC-HCC who underwent curative therapy. Third, the median observation periods in the two groups were relatively short for survival analysis. Larger prospective studies with longer observation periods are thus needed to confirm these results. However, the current study demonstrated that obesity itself was not associated with poor survival in NBNC-HCC patients who underwent curative therapy.

CONCLUSION

Obesity may not need to be taken into account when assessing clinical outcomes after curative therapy in non B non C - hepatocellular carcinoma patients.

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REFERENCES

1. Livraghi T, Mäkisalo H, Line PD. Treatment options in hepatocellular carcinoma today. Scand J Surg 2011; 100: 22-29.
2. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012; 142: 1264-1273.
3. de Lope CR, Tremosini S, Forner A, Reig M, Bruix J. Management of HCC. J Hepatol 2012; 56 Suppl 1: S75-S87.
4. Kaibori M, Ishizaki M, Matsui K, Kwon AH. Clinicopathologic characteristics of patients with non-B non-C hepatitis virus hepatocellular carcinoma after hepatectomy. Am J Surg 2012; 204: 300-307.
5. Yotsuyanagi H, Shintani Y, Moriya K, et al. Virologic analysis of non-B, non-C hepatocellular carcinoma in Japan: frequent involvement of hepatitis B virus. J Infect Dis 2000; 181: 1920-1928.
6. Utsunomiya T, Shimada M. Molecular characteristics of non-cancerous liver tissue in non-B non-C hepatocellular carcinoma. Hepatol Res 2011; 41: 711-721.
7. Ikeda K, Kobayashi M, Someya T, et al. Occult hepatitis B virus infection increases hepatocellular carcinogenesis by eight times in patients with non-B, non-C liver cirrhosis: a cohort study. J Viral Hepat 2009; 16: 437-443.
8. Kusakabe A, Tanaka Y, Orito E, et al. A weak association between occult HBV infection and non-B non-C hepatocellular carcinoma in Japan. J Gastroenterol 2007; 42: 298-305.
9. Tamori A, Nishiguchi S, Kubo S, et al. HBV DNA integration and HBV-transcript expression in non-B, non-C hepatocellular carcinoma in Japan. J Med Virol 2003; 71: 492-498.
10. Umemura T, Kiyosawa K. Epidemiology of hepatocellular carcinoma in Japan.Hepatol Res2007; 37 Suppl 2: S95-S100.
11. Zhou WP, Lai EC, Li AJ, et al. A prospective, randomized, controlled trial of preoperative transarterial chemoembolization for resectable large hepatocellular carcinoma. Ann Surg 2009; 249: 195-202.
12. Nishikawa H, Osaki Y, Kita R, et al. Transcatheter arterial infusion chemotherapy prior to radiofrequency thermal ablation for single hepatocellular carcinoma reduces the risk of intrahepatic distant recurrence. Int J Oncol 2012; 41: 903-909.
13. Nishikawa H, Arimoto A, Wakasa T, Kita R, Kimura T, Osaki Y. Effect of transcatheter arterial chemoembolization prior to surgical resection for hepatocellular carcinoma. Int J Oncol 2013;42:151-160.
14. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003; 348: 1625-1638.
15. WHO: World Health Organization. Fact Sheet for World Wide. Prevalence of Obesity. [(accessed on 27 December 2011)]. Available online: http://www.who.int/mediacentre/factsheets/fs311/en/indexhtml.
16. Caldwell SH, Crespo DM, Kang HS, Al-Osaimi AM. Obesity and hepatocellular carcinoma. Gastroenterology 2004; 127(5 Suppl 1): S97-S103.
17. Wolk A, Gridley G, Svensson M, et al. A prospective study of obesity and cancer risk (Sweden). Cancer Causes Control 2001; 12: 13-21.
18. Møller H, Mellemgaard A, Lindvig K, Olsen JH. Obesity and cancer risk: a Danish record-linkage study. Eur J Cancer 1994; 30A: 344-350.
19. Hassan MM, Hwang LY, Hatten CJ, et al. Risk factors for hepatocellular carcinoma: synergism of alcohol with viral hepatitis and diabetes mellitus. Hepatology 2002; 36: 1206-1213.
20. Obesity-preventing and managing the global epidemic. Report of WHO consultation. World Health Organ Tech Rep Ser 2000;894:1-253.
21. McCurry J. Japan battles with obesity. Lancet 2007; 369: 451-452.
22. Examination Committee of Criteria for 'Obesity Disease' in Japan; Japan Society for the Study of Obesity. New criteria for 'obesity disease' in Japan. Circ J 2002; 66: 987-992.
23. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998; 15: 539-553.
24. Bruix J, Sherman M; Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005; 42: 1208-1236.
25. The general rules for the clinical and pathological study of primary liver cancer. Liver Cancer Study Group of Japan. Jpn J Surg 1989; 19: 98-129.

26. Komura T, Mizukoshi E, Kita Y, et al. Impact of diabetes on recurrence of hepatocellular carcinoma after surgical treatment in patients with viral hepatitis. Am J Gastroenterol 2007;102:1939-1946.
27. Shau WY, Shao YY, Yeh YC, et al. Diabetes mellitus is associated with increased mortality in patients receiving curative therapy for hepatocellular carcinoma. Oncologist 2012;17:856-862.
28. Akiyama T, Mizuta T, Kawazoe S, et al. Body mass index is associated with age-at-onset of HCV-infected hepatocellular carcinoma patients. World J Gastroenterol 2011; 17: 914-921.
29. Muto Y, Sato S, Watanabe A, et al; Long-Term Survival Study (LOTUS) Group. Overweight and obesity increase the risk for liver cancer in patients with liver cirrhosis and long-term oral supplementation with branched-chain amino acid granules inhibits liver carcinogenesis in heavier patients with liver cirrhosis. Hepatol Res 2006; 35: 204-214.
30. Flegal KM, Kit BK, Orpana H, Graubard BI. Association of all-cause mortality with overweight and obesity using standard body mass index categories: a systematic review and meta-analysis. JAMA 2013; 309: 71-82.
31. Peng Y, Rideout D, Rakita S, Lee J, Murr M. Diet-induced obesity associated with steatosis, oxidative stress, and inflammation in liver. Surg Obes Relat Dis 2012; 8: 73-81.
32. Davila JA, Morgan RO, Shaib Y, McGlynn KA, El-Serag HB. Diabetes increases the risk of hepatocellular carcinoma in the United States: a population based case control study. Gut 2005; 54: 533-539.
33. Nishikawa H, Osaki Y, Iguchi E, et al. The Effect of Long-term Supplementation with branched-chain amino acid granules in patients with hepatitis C virus-related hepatocellular carcinoma after radiofrequency thermal ablation. J Clin Gastroenterol 2013;47:359-366.
34. Kobayashi M, Ikeda K, Kawamura Y, et al. High serum des-gamma-carboxy prothrombin level predicts poor prognosis after radiofrequency ablation of hepatocellular carcinoma. Cancer 2009; 115: 571-580.
35. Yao D, Jiang D, Huang Z, et al. Abnormal expression of hepatoma specific gamma-glutamyl transferase and alteration of gamma-glutamyl transferase gene methylation status in patients with hepatocellular carcinoma. Cancer 2000; 88: 761-769.
36. Zhang JB, Chen Y, Zhang B, et al. Prognostic significance of serum gamma-glutamyl transferase in patients with intermediate hepatocellular carcinoma treated with transcatheter arterial chemoembolization. Eur J Gastroenterol Hepatol 2011; 23: 787-793.
37. Yu MC, Chan KM, Lee CF, et al. Alkaline phosphatase: does it have a role in predicting hepatocellular carcinoma recurrence? J Gastrointest Surg 2011; 15: 1440-1449.
38. Ju MJ, Qiu SJ, Fan J, et al. Preoperative serum gamma-glutamyl transferase to alanine aminotransferase ratio is a convenient prognostic marker for Child-Pugh A hepatocellular carcinoma after operation. J Gastroenterol 2009; 44: 635-642.