

Retrospective Cohort Study

Impact of smoking habit on surgical outcomes in non-B non-C patients with curative resection for hepatocellular carcinoma

Keita Kai, Hiroki Koga, Shinichi Aishima, Atsushi Kawaguchi, Koutaro Yamaji, Takao Ide, Junji Ueda, Hirokazu Noshiro

Keita Kai, Shinichi Aishima, Department of Pathology, Saga University Hospital, Saga 849-8501, Japan

Hiroki Koga, Koutaro Yamaji, Takao Ide, Junji Ueda, Hirokazu Noshiro, Departments of Surgery, Saga University Hospital, Saga 849-8501, Japan

Shinichi Aishima, Koutaro Yamaji, Pathology and Microbiology, Saga University Hospital, Saga 849-8501, Japan

Atsushi Kawaguchi, Center for Comprehensive Community Medicine, Saga University Faculty of Medicine, Saga 849-8501, Japan

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Correspondence to: Dr. Keita Kai, MD, Department of Pathology, Saga University Hospital, Nabeshima 5-1-1, Saga City, Saga 849-8501, Japan. kaikit@cc.saga-u.ac.jp
Telephone: +81-952-343264
Fax: +81-952-342055

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Abstract

AIM

To analyzed the correlation between smoking status and surgical outcomes in patients with non-B non-C hepatocellular carcinoma (NBNC-HCC), and we investigated the patients' clinicopathological characteristics according to smoking status.

METHODS

We retrospectively analyzed the consecutive cases of 83 NBNC-HCC patients who underwent curative surgical treatment for the primary lesion at Saga

University Hospital between 1984 and December 2012. We collected information about possibly carcinogenic factors such as alcohol abuse, diabetes mellitus, obesity and smoking habit from medical records. Smoking habits were subcategorized as never, ex- and current smoker at the time of surgery. The diagnosis of non-alcoholic steatohepatitis (NASH) was based on both clinical information and pathological confirmation.

RESULTS

Alcohol abuse, diabetes mellitus, obesity and NASH had no significant effect on the surgical outcomes. Current smoking status was strongly correlated with both overall survival ($P = 0.0058$) and disease-specific survival ($P = 0.0105$) by multivariate analyses. Subset analyses revealed that the current smokers were significantly younger at the time of surgery ($P = 0.0002$) and more likely to abuse alcohol ($P = 0.0188$) and to have multiple tumors ($P = 0.023$).

CONCLUSION

Current smoking habit at the time of surgical treatment is a risk factor for poor long-term survival in NBNC-HCC patients. Current smokers tend to have multiple HCCs at a younger age than other patients.

Key words: Hepatocellular carcinoma; Non-B Non-C; Smoking; Surgery; Prognosis

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Core tip: We retrospectively analyzed the surgical outcomes and clinicopathological characteristics according to smoking habits in consecutive 83 cases with non-B non-C hepatocellular carcinoma (NBNC-HCC) patients who underwent curative surgical treatment for the primary lesion. Current smoking status was strongly correlated with both overall survival and disease-specific survival by multivariate analyses. Subset analyses revealed that current smokers tended to have multiple HCCs at a younger age than other patients. To our knowledge, this is the first report regarding surgical outcomes of NBNC-HCC patients in relation to their smoking status.

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INTRODUCTION

Infections with hepatitis B virus (HBV) and hepatitis C virus (HCV) are well known risk factors for the development of hepatocellular carcinoma (HCC). As

more than 90% of countries around the world have now introduced the HBV vaccine into their national infant immunization schedules, the incidence of HBV-related HCC has been decreasing dramatically^[1]. The development of antiviral therapy can also reduce the incidence of HCV-related HCC^[2]. The number of HCC patients who are negative for both hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCVAb), *i.e.*, those who have so-called "non-B non-C (NBNC) HCC" has rapidly increased in recent years. NBNC HCC patients were reported to account for 24.1% of all HCC patients in a 2010 Japanese survey^[3]. It is thus very important, toward the prevention of HCC, to establish all of the etiologies of NBNC-HCC and to devise countermeasures for it.

The known etiologies of NBNC-HCC are alcoholic liver disease (ALD)^[4], non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH)^[5,6], hemochromatosis^[7], and Budd-Chiari syndrome^[8]; other known etiologies include primary biliary cirrhosis, autoimmune hepatitis, metabolic disease, congestive disease, parasitic disease and unknown etiology^[9]. Emerging epidemiologic data suggest that cigarette smoking may increase the risk of developing HCC^[10-12], but a smoking habit is generally less recognized as a risk factor of developing HCC compared to other etiologies such as ALD and NASH/NAFLD.

Surgery is one of the most important therapeutic measures for HCC. The correlations between surgical outcomes and each etiology of HCC are very important because knowing these correlations will provide the motivation and strategies for the prevention of each specific etiology. The clinicopathological characteristics and surgical outcomes of patients with HBV-HCC and HCV-HCC have been well investigated^[13-15]. There are also many studies comparing the surgical outcomes or clinicopathological characteristics of patients with NBNC-HCC and those with viral-associated HCC or between each etiology of NBNC-HCC^[16-29]. However, no study has addressed the impact of smoking habit on surgical outcomes or clinicopathological characteristics according to smoking habits in patients with NBNC-HCC, to our knowledge.

In the present study we analyzed the correlation between smoking status and surgical outcomes in patients with NBNC-HCC, and we investigated the patients' clinicopathological characteristics according to smoking status.

MATERIALS AND METHODS

Patients

The study protocol was approved by the Ethics Committee of the Faculty of Medicine at Saga University (approval no. 28-23). The initial enrollees in the study were 477 consecutive patients with HCC who underwent curative surgical treatment for the primary lesion at Saga University Hospital between 1984 and

Table 1 Clinicopathologic features of the patients with non-B non-C hepatocellular carcinoma (*n* = 83)

Characteristic		<i>n</i> (%)
Age, yr (mean ± SD)		66.4 ± 11.6
Gender	Male	66 (79.5)
	Female	17 (20.5)
Alcohol abuse	(+)	19 (22.9)
	(-)	64 (77.1)
Smoking habit	Never	36 (43.4)
	Ex	23 (27.7)
	Current	24 (28.9)
Diabetes mellitus	(+)	29 (34.9)
	(-)	54 (65.1)
Obesity	(+)	26 (31.3)
	(-)	57 (68.7)
BMI (mean ± SD)		22.8 ± 4.50
Tumor size (mean ± SD mm)		65.2 ± 41.4
Solitary/Multiple	Solitary	52 (62.7)
	Multiple	31 (37.3)
Vp	(+)	32 (38.6)
	(-)	51 (61.4)
Background liver fibrosis ¹	F0	16 (19.5)
	F1	21 (25.6)
	F2	10 (12.2)
	F3	18 (22.0)
	F4	17 (20.7)
NASH ¹	(+)	10 (12.2)
	(-)	72 (87.8)

¹Noncancerous liver tissue was not available in one case (*n* = 82). NASH: Non-alcoholic steatohepatitis. Vp: Portal vein invasion.

December 2012. Of these patients, we retrospectively examined the cases of the 83 patients who were both non-B (HBsAg-negative) and non-C (HCVAb-negative) in serological tests. One patient with Budd-Chiari syndrome and another patient with Dubin-Johnson syndrome were included. Written informed consent was obtained from all patients for the use of their clinical information.

Analyses of alcohol abuse, obesity, diabetes mellitus and smoking status

Alcohol abuse was defined as a daily ethanol intake > 40 g for men and > 20 g for women. Obesity was defined as a body mass index (BMI) > 25 kg/m² in both genders. Smoking status was categorized as never smoker, ex-smoker and current smoker at the time of surgery. A current smoker was defined as an individual who regularly smoked and continued to smoke within 1 year prior to the surgery. An ex-smoker was defined as an individual who quit smoking at least 1 year before his or her surgery^[30]. Only patients who were clinically diagnosed as having diabetes mellitus were categorized as being in the present diabetes mellitus group. All of this information was collected from medical records.

Histopathological analysis

The histopathological diagnosis and classification were performed by two pathologists (Kai K and Aishima

S). The degree of fibrosis in noncancerous liver tissues was assessed according to the new Inuyama classification system which is widely used in Japan, as follows: F0, no fibrosis; F1, portal fibrosis widening; F2, portal fibrosis widening with bridging fibrosis; F3, bridging fibrosis plus lobular distortion; and F4, liver cirrhosis^[31]. In one case the fibrosis could not be assessed because of an insufficiency of noncancerous liver tissue. The diagnoses of NASH were based on both clinical information and pathological confirmation.

Statistical analyses

We used JMP ver. 12.2 software and SAS software ver. 9.4 (SAS Institute, Cary, NC, United States) for the statistical analyses. The comparisons of pairs of groups were performed using Student's *t*-test, the χ^2 test and Fisher's exact test, as appropriate. Disease-free survival (DFS) was determined as the length of time after surgery that the patient survived without new lesions of HCC. Overall survival (OS) was determined from the time of surgery to the time of death or the most recent follow-up. Disease-specific survival (DSS) was determined from the time of surgery to the time of cancer-related death or most recent follow-up.

Cox proportional hazards modeling was applied for uni- and multivariate analyses. The purpose of the multivariate analysis was to adjust potential covariates for the comparison of smoking status; then, age, gender, portal vein invasion, T factor and multiple tumors were always kept in the model and others were selected by the stepwise procedure with the *P* value threshold of 0.2. Postoperative survival curves were calculated using the Kaplan-Meier method. Differences in survival curves were compared using the log-rank test. Values of *P* < 0.05 were considered significant. All statistical analyses were supervised by the statistician co-author (Kawaguchi A).

RESULTS

Clinicopathological features and risk factors of NBNC-HCC

The clinicopathological features of the 83 cases of NBNC-HCC are summarized in Table 1. The patients were 66 men and 17 women with a mean age at the time of surgery of 66.4 years. Nineteen patients (22.9%) were etiologically categorized into the alcohol abuse group; 29 patients (34.9%) had diabetes mellitus, and 26 patients (31.3%) were judged to be obese. Ten patients (12.2%) were pathologically confirmed as having NASH. Thirty-six patients (43.4%) were categorized into the never-smoker group and 23 (27.7%) into the ex-smoker group and the remaining 24 patients (28.9%) were currently smoking at the time of their surgery. The smoking cessation periods of the ex-smokers were as follows: 1-5 years, two patients; 5-10 years, four patients; and > 10 years, 17 patients.

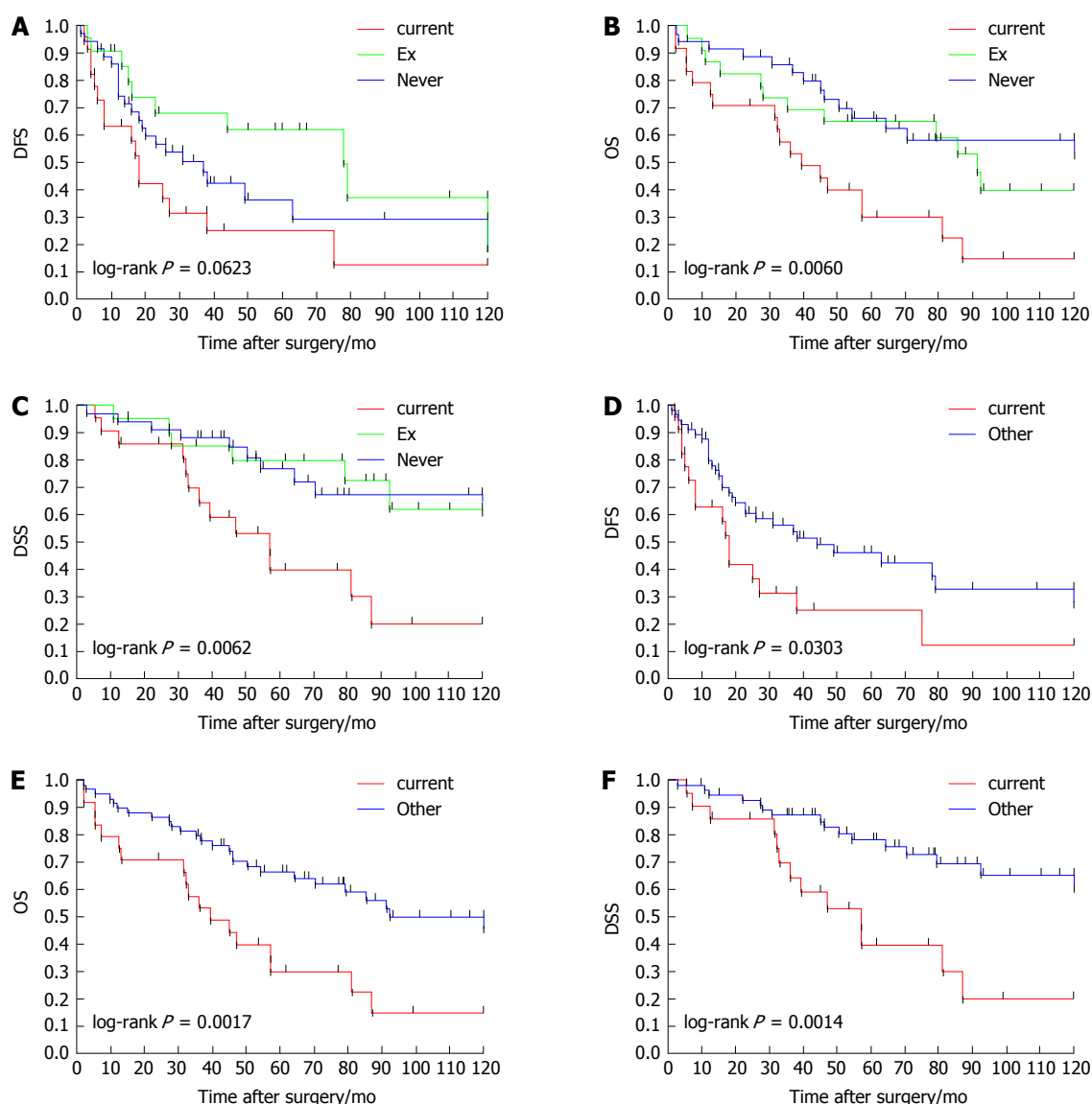


Figure 1 Survival curves of disease-free survival, overall survival and disease-specific survival according to smoking habit (never, Ex and current) or current smoking habit (current and other). A-C: Kaplan-Meier curves according to smoking habit (current, Ex and never) for disease-free survival (DFS), overall survival (OS) and disease-specific survival (DSS); D-F: Kaplan-Meier curves according to smoking habit (current and other) for DFS, OS and DSS.

Univariate analyses for DFS, OS and DSS

The results of the univariate analyses for DFS, OS and DSS by Cox's proportional hazards model are summarized in Table 2. The factors significantly correlated with DFS were smoking (Ex vs current, $P = 0.0271$), smoking (current vs other, $P = 0.035$), portal vein invasion ($P = 0.0035$), T factor ($P = 0.0004$), and multiple tumors at the time of surgery ($P = 0.0001$). No patient had received adjuvant therapy after curative surgery until recurrence.

The factors significantly correlated with OS were smoking (Ex vs current, $P = 0.0349$), smoking (current vs never, $P = 0.0034$), smoking (Ex + current vs never, $P = 0.0436$), smoking (current vs other, $P = 0.0024$), portal vein invasion ($P = 0.0362$), and multiple tumors at the time of surgery ($P = 0.0211$). The factors significantly correlated with DSS were smoking [Ex vs current, $P = 0.0155$, smoking (current vs never, $P =$

0.0092], smoking (current vs other; $P = 0.0025$), T factor ($P = 0.0364$) and multiple tumors at the time of surgery ($P = 0.0065$). The survival curves of DFS, OS and DSS according to smoking habit (never, Ex and current) or current smoking habit (current and other) are provided as Figure 1. The current-smoking group showed significantly poor survival curves compared to all other patient groups in each analysis of DFS, OS and DSS.

Multivariate analyses for DFS, OS and DSS

The results of the multivariate analyses for DFS, OS and DSS by Cox's proportional hazards model are summarized in Table 3. The only factor that was significantly correlated with DFS was portal vein invasion ($P = 0.0229$). The factors significantly correlated with OS were smoking (current vs other) and portal vein invasion ($P = 0.0058$ and $P = 0.0061$, respectively). The

Table 2 Univariate analyses for disease-free survival, overall survival and disease-specific survival after hepatic resection

	DFS		OS		DSS	
	HR (95%CI)	P value	HR (95%CI)	P value	HR (95%CI)	P value
Age (≤ 70 yr)	0.777 (0.434-1.389)	0.3948	0.959 (0.529-1.739)	0.8915	0.757 (0.360-1.591)	0.4622
Gender (male)	0.742 (0.382-1.443)	0.3796	1.466 (0.653-3.291)	0.3537	1.351 (0.515-3.545)	0.5404
Occult HBV infection	1.052 (0.564-1.961)	0.8736	1.184 (0.628-2.232)	0.6009	1.328 (0.625-2.821)	0.4604
Alcohol abuse	0.700 (0.326-1.503)	0.3605	1.492 (0.749-2.969)	0.2549	1.489 (0.631-3.514)	0.3639
Smoking (Ex <i>vs</i> current)	0.405 (0.182-0.903)	0.0271	0.451 (0.215-0.945)	0.0349	0.299 (0.113-0.795)	0.0155
Smoking (Ex <i>vs</i> never)	0.680 (0.319-1.453)	0.3197	1.295 (0.597-2.807)	0.5132	0.905 (0.328-2.501)	0.848
Smoking (current <i>vs</i> never)	1.680 (0.874-3.230)	0.1199	2.869 (1.417-5.807)	0.0034	3.026 (1.315-6.968)	0.0092
Smoking (Ex + current <i>vs</i> never)	1.078 (0.606-1.920)	0.7976	1.926 (1.019-3.640)	0.0436	1.735 (0.804-3.745)	0.1604
Smoking (current <i>vs</i> other)	1.926 (1.047-3.544)	0.035	2.569 (1.397-4.724)	0.0024	3.144 (1.497-6.604)	0.0025
Diabetes mellitus	0.894 (0.474-1.685)	0.7285	1.715 (0.941-3.126)	0.0779	1.414 (0.665-3.008)	0.3681
Pathological NASH	1.222 (0.516-2.892)	0.649	1.076 (0.423-2.736)	0.8781	1.342 (0.465-3.873)	0.5863
Obesity	0.989 (0.535-1.828)	0.9714	1.049 (0.556-1.981)	0.8827	1.183 (0.549-2.549)	0.6673
Fibrosis	1.163 (0.699-1.936)	0.5608	1.004 (0.583-1.729)	0.9883	1.407 (0.742-2.670)	0.2956
Vp	2.428 (1.338-4.407)	0.0035	1.892 (1.042-3.436)	0.0362	1.918 (0.919-4.002)	0.0828
T factor (T3/4 <i>vs</i> T1/2)	3.220 (1.680-6.169)	0.0004	1.793 (0.984-3.268)	0.0565	2.222 (1.052-4.693)	0.0364
Multiple tumors	3.275 (1.784-6.014)	0.0001	2.009 (1.110-3.636)	0.0211	2.767 (1.329-5.761)	0.0065

Vp: Portal vein invasion; DFS: Disease-free survival; DSS: Disease-specific survival; HBV: Hepatitis B virus; NASH: Non-alcoholic steatohepatitis; OS: Overall survival.

Table 3 Multivariate analyses for current smokers *vs* other (age, gender, Vp, T factor in, $P = 0.2$)

Type	Label	HR (95%CI)	P value
DFS	Smoking (current <i>vs</i> other)	1.897 (0.888-4.054)	0.0985
	Age (≤ 70 yr)	0.627 (0.330-1.191)	0.1535
	Gender (male)	0.611 (0.279-1.337)	0.2176
	Vp	2.656 (1.145-6.165)	0.0229
	T factor (T3/4 <i>vs</i> T1/2)	1.574 (0.537-4.609)	0.4083
	Multiple tumors	1.930 (0.807-4.614)	0.1394
	Alcohol abuse	0.547 (0.228-1.310)	0.1755
OS	Smoking (current <i>vs</i> other)	2.807 (1.349-5.840)	0.0058
	Age (≤ 70 yr)	1.189 (0.603-2.346)	0.6177
	Gender (male)	1.362 (0.555-3.343)	0.4999
	Vp	3.069 (1.377-6.839)	0.0061
	T factor (T3/4 <i>vs</i> T1/2)	0.532 (0.187-1.512)	0.2364
DSS	Multiple tumors	1.830 (0.760-4.405)	0.1774
	Smoking (current <i>vs</i> other)	3.133 (1.307-7.512)	0.0105
	Age (≤ 70 yr)	0.988 (0.424-2.302)	0.9775
	Gender (male)	1.406 (0.463-4.271)	0.5478
	Vp	2.756 (1.095-6.935)	0.0313
	T factor (T3/4 <i>vs</i> T1/2)	0.610 (0.167-2.233)	0.4555
	Multiple tumors	2.476 (0.797-7.693)	0.1169
	Pathological NASH	2.320 (0.689-7.811)	0.1741

DFS: Disease-free survival; DSS: Disease-specific survival; OS: Overall survival; Vp: Portal vein invasion.

factors significantly correlated with DSS were smoking (current *vs* other) and portal vein invasion ($P = 0.0105$ and $P = 0.0313$, respectively).

Subset analysis between the current smokers and the other patients

To clarify the characteristics of the current smokers, we further performed subset analyses regarding the clinicopathological factors, treatment and causes of death (Table 4). The current smokers were significantly younger than the Never + Ex patient group (mean age 59.4 year *vs* 69.3 year, $P = 0.0002$) at the time of

surgery. The current smokers group had significantly greater incidences of alcohol abuse ($P = 0.0188$) and multiple tumors ($P = 0.023$). No significant difference was observed in gender, diabetes mellitus, obesity, indocyanine green retention rate at 15 min (ICG R15), tumor size, portal vein invasion, T factor, serum AFP level or liver fibrosis.

Thirteen of the 24 patients (54.2%) in the Current smoking group died of HCC, whereas 17 of the 59 patients (28.8%) in the Never + Ex patient group died of HCC ($P = 0.0293$). Five of the 24 patients (20.8%) in the Current smoking group died of other causes: cerebral hemorrhage, surgical complication for gastric cancer, pneumoniae (two cases) and sepsis due to pseudomembranous colitis.

In the Never + Ex group, 11 of the 59 patients (18.6%) died of other causes: other malignancy, four patients (two cases of bile duct cancer, prostatic cancer, malignant lymphoma); cerebral infarction, two patients; liver failure, two patients; pneumonia, one patient; sudden cardiac death, one patient and renal failure, one patient.

DISCUSSION

To determine the influence of etiological differences on the outcomes of the surgical treatment for HCC, many studies have compared surgical outcomes between patients with NBNC-HCC and those with viral-associated HCC, but the results are controversial. Some studies showed that surgical outcomes in patients with NBNC-HCC were not significantly different compared to those of patients with hepatitis virus-related HCC^[17,20,23,29]. Other studies reported that NBNC-HCC patients had significantly better surgical outcomes than HCV-HCC patients^[18,24,26]. In a recent Japanese nationwide study of 2738 NBNC-HCC patients, the

Table 4 Comparison of current smoking status and clinicopathological factors (*n* = 83)

	Current (<i>n</i> = 24)	Never + Ex (<i>n</i> = 59)	<i>P</i> value
Age, yr (mean ± SD)	59.4 ± 12.0	69.3 ± 10.2	0.0002
Gender (male/female)	22/2	44/15	0.0803
Alcohol abuse (+/-)	10/14	9/50	0.0188
Diabetes mellitus (+/-)	8/16	21/38	0.8448
Obesity (+/-)	6/18	20/39	0.6024
ICG R15 (%)	11.7 ± 1.8	14.8 ± 1.2	0.1235
Tumor size (mean ± SD mm)	68.4 ± 44.0	63.9 ± 40.6	0.6724
Solitary/Multiple	10/14	42/17	0.023
Vp (+/-)	9/15	23/36	0.8998
T factor (T12/T34)	10/24	33/26	0.3329
AFP (mean ± SD)	4450 ± 14563.6	3235 ± 13042	0.6442
Fibrosis (F12/F34, <i>n</i> = 82)	11/13	36/22	0.2224
Recurrence (+/-)	16/8	32/27	0.3362
Therapy for recurrent tumor (+/-) ¹	14/2	27/5	0.7724
TAE only	11	14	
Surgical resection	1	5	
Ablation	1	2	
Chemotherapy	1	3	
Multiple therapy ²	0	3	
Tumor-related death (%)	13 (54.2)	17 (28.8)	0.0293
Other cause of death (%)	5 (20.8)	11 (18.6)	0.8187

¹Comparison restricted in recurrent case; ²Two cases of TAE + operation and one case of TAE + ablation. ICG R15: Indocyanine green retention rate at 15 min; TAE: Transcatheter arteriography embolization; Vp: Portal vein invasion.

DFS of the NBNC-HCC group was significantly better than those of the HBV-HCC and HCV-HCC groups^[16]. For the purpose of clarifying the association between smoking status and surgical outcomes, we focused on NBNC-HCC in the present study because the surgical outcomes of viral-associated HCC may be influenced by cirrhosis due to viral-associated hepatitis.

Many studies have been reported regarding surgical outcomes and etiologies of NBNC-HCC. The relationships between the surgical outcomes of NBNC-HCC and metabolic diseases such as obesity, diabetes mellitus and NAFLD/NASH have been extensively investigated. Several investigations indicated favorable surgical outcomes of NBNC-HCC associated with NAFLD/NASH compared to those of viral-associated HCC^[21-32]. It was reported that obesity did not affect survival in patients with NBNC-HCC after curative therapy^[29]. In contrast, a large retrospective Japanese multicenter cohort study of 5326 patients with NBNC-HCC indicated that patients with BMI values > 22 and ≤ 25 kg/m² showed the best prognoses compared to other BMI categories, after adjusting for age, gender, tumor-related factors, and Child-Pugh score^[3]. However, these previous studies regarding the surgical results of NBNC-HCC patients did not involve an analysis of smoking habit despite the recognition of smoking as risk factor for NBNC-HCC. We therefore focused on the smoking habit in the present study.

The major finding of the present study is the strong correlation between smoking habit and surgical outcomes. Although emerging epidemiologic data suggest that cigarette smoking may increase the risk of HCC^[10-12], the influence of cigarette smoking on HCC survival has not been well documented. We were able to find 10 studies in the English literature that analyzed the correlation of smoking and HCC mortality^[33-42]. Large cohort studies indicating an impact of smoking habit on HCC mortality have been reported from Japan^[33,34], the United Kingdom^[35], China^[36] and Taiwan^[37-39]. In contrast, several studies reported a negative correlation between HCC mortality and smoking habit, although those studies analyzed relatively small numbers of HCC cases (262-552 cases)^[40-42].

Most of the previous studies regarding HCC mortality and smoking habit did not focus on the surgical outcomes of HCC patients or distinguish surgical cases versus nonsurgical cases. We were able to identify only two reports from China that focused on surgical outcomes of HCC patients: Zhang *et al.*^[30] analyzed the outcomes of 302 patients with HBV infection who had undergone surgical resection for HCC, and their findings revealed a significant influence of smoking status on both recurrence and mortality. Lv *et al.*^[43] investigated the outcomes of 425 patients with a predominant population (74%) of HBV infection who were undergoing hepatectomy for HCC, and those authors' analysis revealed that cigarette smoking is an independent risk factor for the development of liver-related and infectious complications. We were unable to find any other study reporting the surgical outcomes of NBNC-HCC patients in relation to their smoking status.

In the present study, the survival of the current smokers was significantly poorer than that of the never-smokers, and no significant difference in the survival of the ex-smokers and never-smokers was revealed. We speculate that the reason for the latter finding is due to the long cessation period (> 10 years) for most of the ex-smokers. Our subset analyses comparing the current smokers and the other patients revealed that the current smokers were significantly younger and were more likely to have multiple tumors at the time of surgery. These findings suggest that a smoking habit may affect multicentric liver carcinogenesis. The underlying mechanism of liver carcinogenesis induced by smoking is as yet unclear and should be investigated in further studies.

Generally, alcoholic abuse is known as a poor-prognosis risk factor in surgical treatment for HCC because of the poor liver function of individuals who abuse alcohol. Indeed, in the present study the proportion of alcohol-abusing patients was higher in the current smoking group, but no significant between-group difference was observed in liver function as represented by the ICG R15 or liver fibrosis. Notably, over half of our study's current-smoker patients died of HCC, and only five of the current smokers died of other causes. Thus, the causes of death in the current-

smoker group were significantly different from those of the other patient groups.

Although current smoking was significantly correlated with DFS in our univariate analysis, no such significance was observed in the multivariate analyses, whereas current smoking showed significant correlations with the OS and DSS in the multivariate analyses. One possible reason for this is our study's small sample size. Another possible reason is that the malignant potential of the recurrent tumors in the current-smoker group may be different from those of the other groups, because the survival after recurrence was significantly different despite the lack of a significant difference in the recurrence rate and the treatments for the recurrent tumors between the current-smoker group and the other groups.

The limitations of the present study are its retrospective design, the relatively small number of patients, and the long study period for enrollment. In addition, information about our patients' post-surgery smoking status was not available, and thus the effects on survival of a smoking habit after surgery and a smoking habit after recurrence could not be examined. It remains quite regrettable that the previous large case series and multicenter studies did not investigate the HCC patients' smoking status. We hope a larger prospective study verifies the precise influence of smoking on the survival of patients with NBNC-HCC, as its results can be expected to provide further motivation for smoking cessation.

In conclusion, the results of our single-institute retrospective study indicate that current smoking habit is significantly correlated with the surgical outcomes of patients with NBNC-HCC. Our analyses also revealed that the current smokers were significantly younger than the other patient groups and had significantly greater incidences of alcohol abuse and multiple tumors at the time of surgery.

COMMENTS

Research frontiers

No previous study has addressed the impact of smoking habit on surgical outcomes or clinicopathological characteristics according to smoking habits in patients with non-B non-C hepatocellular carcinoma (NBNC-HCC).

Innovations and breakthroughs

The novel findings of this study are (1) current smoking habit at the time of surgical treatment is a risk factor for poor long-term survival in NBNC-HCC patients; and (2) current smokers tend to have multiple HCCs at a younger age than other patients.

Applications

The results of present study can be expected to provide further motivation for smoking cessation.

Terminology

NBNC-HCC is defined as hepatocellular carcinoma that has arisen in an individual who is negative for both hepatitis B surface antigen and hepatitis C antibody. Alcohol abuse was defined as a daily ethanol intake > 40 g for men and > 20 g for women. Obesity was defined as a body mass index > 25 kg/m²

in both genders. A current smoker was defined as an individual who regularly smoked and continued to smoke within 1 year prior to the surgery. An ex-smoker was defined as an individual who quit smoking at least 1 year before his or her surgery.

Peer-review

An interesting paper about risk factors in patients with NBNC hepatocellular cancer. Results are adequate and conclusions are very clear.

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